

THE SERONEGATIVE SPONDARTHROITIDES :
A CLINICAL AND GENETIC STUDY WITH PARTICULAR
REFERENCE TO THE HISTOCOMPATIBILITY ANTIGENS

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SUMMARY

In a clinical, radiological and histocompatibility typing study of 360 patients the association between individual types of seronegative spondarthritis and HLA-B27 is confirmed.

HLA-B27 was associated with recurrent acute anterior uveitis in 119 patients with ankylosing spondylitis, but not with severity of the spinal disease. HLA-B27 negative patients had a later mean age of onset and more dactylitis of the toes. In 77 patients with Reiter's syndrome the presence of HLA-B27 was associated with the occurrence of keratoderma blenorrhagica, acute anterior uveitis and radiological sacroiliitis but not with conjunctivitis. No particular pattern of peripheral psoriatic arthritis was associated with HLA-B27 in the 79 patients studied. The frequency of HLA-B27 was highest in psoriatic patients with spinal arthritis.


In 22 patients with peripheral psoriatic arthritis in addition to spinal arthritis the frequency of HLA-B27 was significantly less than in 8 psoriatic patients with spinal arthritis alone and in 119 patients with ankylosing spondylitis alone. In patients with chronic inflammatory bowel disease and ankylosing spondylitis the frequency of HLA-B27 was significantly less than in 119 patients with ankylosing spondylitis alone. These results were confirmed by a combined analysis with other series and suggest the possible role of genetic factors predisposing to chronic inflammatory bowel disease and peripheral psoriatic arthritis also predisposing to ankylosing spondylitis in HLA-B27 negative individuals.

In a study of 36 selected families only 2 examples of seronegative spondylarthritis in HLA-B27 negative relatives were seen. In both families there was evidence of the possible role of genes predisposing to chronic inflammatory bowel disease.

In a study of 23 unselected families of probands with ankylosing spondylitis this disease was found in 28.6% of HLA-B27 positive fathers, none of the mothers and none of the HLA-B27 negative parents. Comparison with the frequency of ankylosing spondylitis in blood donors and of reactive arthritis in infected individuals suggests that additional genetic factors may be necessary for the occurrence of disease.

A study of three pairs of identical twins showed discordance for ankylosing spondylitis in two suggesting the necessity of environmental factors in addition to genetic ones for the development of disease.

In accordance with the regulations of the University of Edinburgh, I declare that this thesis has been composed by myself, and that the work reported in it is my own except where due acknowledgement has been made to the contribution of others.


~~CLIFFORD JOHN EASTMOND~~

CHAPTER 1

AIMS OF THE PRESENT STUDY

In 1973 two independent groups almost simultaneously reported on a high association between the histocompatibility antigen HLA-B27 and ankylosing spondylitis (Brewerton et al, 1973(a); Schlosstein et al, 1973). The Westminster group subsequently reported an increased frequency of HLA-B27 in patients with Reiter's syndrome (Brewerton et al, 1973(b)), psoriatic arthritis and ankylosing spondylitis in association with ulcerative colitis (Brewerton et al, 1974). An increased frequency of HLA-B27 was also found in ankylosing spondylitis associated with Crohn's disease (Nagant de Deuxchaisnes, 1974) and in juvenile chronic polyarthritis (Edmonds et al, 1974).

The importance of genetic factors in ankylosing spondylitis is well known (de Blécourt, Polman and de Blécourt-Meindersma, 1961; Emery and Lawrence, 1967). The evidence for genetic interrelation between the diseases found to have a high frequency of HLA-B27 has been reviewed by Wright (1975).

The present study was initiated to:

- (1) confirm the association between HLA-B27 and this group of diseases
- (2) by detailed clinical and radiological study to examine those features of each disease associated with HLA-B27
- (3) by the study of informative families
 - (i) to determine if multiple cases in relatives were associated with HLA-B27

- (ii) to determine the prevalence of ankylosing spondylitis and radiological sacroiliitis in first degree HLA-B27 positive relatives of patients with ankylosing spondylitis.

It was hoped by this form of study of individual cases and their families to obtain further information as to:

- (1) how the association between HLA-B27 and this group of diseases may have occurred.
- (2) Whether other genetic or environmental factors were necessary for the development of these diseases.

CHAPTER 2

INTRODUCTION AND LITERATURE REVIEW

2.1 FAMILIAL AGGREGATION OF INDIVIDUAL RHEUMATIC DISEASES

2.1.1 Ankylosing Spondylitis

In a study of 18 selected families of patients with ankylosing spondylitis, 13 further affected individuals were found in ten families (Rogoff and Freyberg, 1949). However, no control population was studied for comparison. From a study of a hospital population in Bristol, West (1949) found a higher prevalence of ankylosing spondylitis in relatives of affected probands than in the general population. His figure for the population prevalence of ankylosing spondylitis (1 in 2,000), however, was based on hospital diagnosed patients and an estimated allowance made for cases missed by this method of selection.

The first study in which an adequate comparative clinical and radiological study of patients and controls families was performed was reported by de Blécourt, Polman and de Blécourt-Meindersma (1961). They had studied the first degree relatives of probands with ankylosing spondylitis, rheumatoid arthritis and without either disease. Their results showed an overall prevalence in first degree male relatives of probands with ankylosing spondylitis of 6.4% compared with 0.4% in the control families. The prevalence in first degree female relatives of ankylosing spondylitis probands was lower (3.0%) but no disease was found in the female relatives of the control families.

Emery and Lawrence (1967) compared the results of their detailed clinical and radiological study of first degree relatives of probands with ankylosing spondylitis with population controls studied under similar circumstances. In an earlier population study of Leigh and Wensleydale (Lawrence, 1963) ankylosing spondylitis had been diagnosed in 0.4% of males over the age of 15 years. No cases were found in 1,173 females. These figures compare with a prevalence in first degree relatives of 5.26% of male relatives and 1.71% of female relatives. Similarly radiological sacroiliitis was found in 19.5% of male and 8.3% of female first degree relatives compared with population prevalence of 4.9% and 1.5% respectively (Ansell and Lawrence, 1965).

These two studies firmly confirmed the importance of genetic factors in ankylosing spondylitis.

2.1.2 Psoriatic Arthritis

Few similarly detailed family studies of psoriatic arthritis have been performed. The largest and most satisfactory (Moll and Wright, 1973(a)) was of the first degree relatives of 88 patients with psoriatic arthritis, of whom 8.3% had clinical psoriatic arthritis compared with none in 79 spouse controls.

2.1.3 Reiter's Syndrome

Individual examples of multiple cases of Reiter's syndrome within families have been reported (Paronen,

1948; Gough, 1962; Mowat and Nicol, 1968). Lawrence (1974), however, in his study of the families of 35 probands with Reiter's syndrome found no secondary cases of Reiter's syndrome, though he comments on the obvious difficulties in such a study of a venereally acquired disease. Previous episodes of mild examples of Reiter's syndrome having been forgotten or deliberately not mentioned by relatives.

2.2 ASSOCIATIONS BETWEEN INDIVIDUAL DISEASES

Ankylosing spondylitis and radiological sacroiliitis have been shown to occur more frequently in patients with psoriatic arthritis (Wright, 1961), ulcerative colitis (Wright et al, 1965; Wright and Watkinson, 1965; Macrae and Wright, 1973), Crohn's disease (Ansell and Wigley, 1964; Haslock, 1973; Deshayes et al, 1976), Reiter's syndrome (Csonka, 1959; Good, 1965; Lawrence, 1974) and uveitis (Lenoch, Králik and Bartos, 1959; Catterall, 1959) compared with the general population. The Leeds group have produced evidence that psoriasis is more prevalent in patients with ulcerative colitis and Crohn's disease (Wright and Moll, 1976). Similarly Ansell and Wigley (1964) found five of their 91 patients with Crohn's disease to have psoriasis. Although they did not study a control group this is certainly higher than the generally accepted prevalence of 1-2% (Ingram, 1954). In addition true overlap syndromes have been described in which one

disease appears to develop into another. Perhaps the best known and universally recognised example is Reiter's syndrome and psoriatic arthritis (Wright and Reed, 1964).

2.3 FAMILIAL AGGREGATION BETWEEN INDIVIDUAL DISEASES

Hammer, Ashurst and Naish (1968) in a family study of inflammatory bowel disease found an increased prevalence of ulcerative colitis and Crohn's disease in the families of probands with Crohn's disease and ulcerative colitis respectively. In addition they found several families with undiagnosed polyarthritis.

The results of four detailed family studies of psoriatic arthritis (Moll and Wright, 1973(a)), ulcerative colitis (Macrae and Wright, 1973), Crohn's disease (Haslock, 1973) and Reiter's syndrome (Lawrence, 1974) are given in Table 2.1 demonstrating the associations between these individual diseases within families.

2.4 THE CONCEPT OF SERONEGATIVE SPONDARTHROITIDES

The term seronegative spondarthritides has been suggested to apply to the arthropathies of ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, ulcerative colitis, Crohn's disease, Whipple's disease and Behçet's syndrome (Moll et al, 1974).

These arthropathies have been included within this term on the basis of the clinical similarities

Table 2.1 Reported prevalence of ankylosing spondylitis, radiological sacroiliitis, chronic inflammatory bowel diseases, psoriasis and psoriatic arthritis in the first degree relatives of probands with psoriatic arthritis, ulcerative colitis, Crohn's disease, Reiter's syndrome and in the general population.

Disease	Prevalence (%) in first degree relatives of probands with				Prevalence (%) in population controls(5)
	Psoriatic arthritis(1)	Ulcerative colitis(2)	Crohn's disease(3)	Reiter's syndrome(4)	
Radiological sacroiliitis	8.0	4.7	6.2	8.8	1.1
Ankylosing spondylitis	4.2	3.2	0	2.9	0.19
Ulcerative colitis	0.9	1.0	0	no data	0.06
Crohn's disease	0	0	1.4	no data	0.01
Psoriasis	19.7	4.1	2.0	6.4	1.10
Psoriatic arthritis	5.4	0	0	1.8 (polyarthritis)	0.10

Data from: (1) Moll and Wright (1973(a)); (2) Macrae and Wright (1973); Haslock (1973); (4) Lawrence (1974); Wright (1975).

between them, the association of radiological sacroiliitis and ankylosing spondylitis with all of them and the clinical overlaps seen between them both in individual patients and in groups of patients. In addition these associations are considered to be at least partly genetic in origin in view of the higher prevalence of each in relatives of probands with other members of the groups (Table 2.1).

Whipple's disease and Behçet's syndrome have been included by the Leeds group though the comparative rarity of these two disorders means that detailed studies of large numbers of patients has not been possible. A recent family study of Behcet's syndrome (Chamberlain, 1977) failed to find any patients or relatives with radiological sacroiliitis or ankylosing spondylitis. In view of their rarity and absence of firm genetic links with the other members of the group of disorders they have not been included in this current study.

2.5 HISTOCOMPATIBILITY ANTIGEN ASSOCIATIONS IN THE SERONEGATIVE SPONDARTHROITIDES

In 1973 two independent groups both reported, within a few weeks of each other a high frequency of the histocompatibility antigen HLA-B27 in unrelated patients with ankylosing spondylitis (Brewerton et al, 1973(a); Schlosstein et al, 1973). Ninety-six per cent of the Westminster Hospital's patients compared with 4% of blood donor controls, and 88% of

the Los Angeles patients compared with 8% of blood donor controls were HLA-B27 positive. Confirmation that this association was not due to interference with the method of testing or of the cells surface membranes as a result of the disease itself or its therapy was excluded by the finding of the same antigen, HLA-B27, in 50% of tested first degree relatives (Brewerton et al, 1973(a)).

Knowledge of the clinical and genetic inter-relations between individual diseases in this group led to the finding of an increased frequency of HLA-B27 in patients with Reiter's syndrome (Brewerton et al, 1973(b); Morris et al, 1974), psoriatic arthritis (Brewerton et al, 1974), ankylosing spondylitis associated with ulcerative colitis (Brewerton et al, 1974; Morris et al, 1974), ankylosing spondylitis associated with Crohn's disease (de Deuxchaisnes et al, 1974) and acute anterior uveitis (Brewerton, 1975). An increased frequency of HLA-B27 was also reported in juvenile chronic polyarthritis associated with ankylosing spondylitis or radiological sacroiliitis but not in juvenile seropositive rheumatoid arthritis (Edmonds et al, 1974). Twenty per cent of patients with juvenile chronic polyarthritis but without spinal or sacroiliac disease were also found to be HLA-B27 positive. Similar results have been obtained by other groups (Veys et al, 1976; Sturrock et al, 1974; Gershwin et al, 1977).

No association has been demonstrated between ulcerative colitis without spinal disease and HLA-B27 (Brewerton et al, 1974; Morris et al, 1974; Hyla, Frank and Davis, 1976; Mallas et al, 1976; Bergman et al, 1976) and Crohn's disease without spinal disease (Russel et al, 1974; Deshayes et al, 1976; Hyla, Frank and Davis, 1976; Mallas et al, 1976; Huaux et al, 1977; Bergman et al, 1976). One of these studies (Mallas et al, 1976) showed a higher frequency of HLA-B27 in patients with total colonic involvement by either ulcerative colitis or Crohn's disease.

2.6 HISTOCOMPATIBILITY ANTIGENS: GENETICS AND NOMENCLATURE

In the 1950's it was recognised that blood transfusions could induce the formation of agglutinating antibodies directed at human leucocyte antigens (Goudsmit and van Longheim, 1953; Dausset, 1954; Payne, 1957; and van Longheim et al, 1953). Subsequently similar antibodies were found in the sera of pregnant women (van Rood, van Leeuwen and Eeruisse, 1959; Payne and Rolfs, 1958; and van Rood, Eeruisse and van Leeuwen, 1958). The analysis of the reaction patterns of these antisera with human leucocytes was facilitated by the use of computers (van Rood and van Leeuwen, 1963). These analyses concluded that there were two independent but closely linked genetic loci now termed HLA-A and HLA-B (Histocompatibility Testing, 1967; WHO-IUIS Terminology Committee, 1975).

Confirmation that these loci are distinct from each other has been shown by the occurrence of infrequent genetic recombinants (Kissmeyer-Nielsen, Svejgaard and Ahvons, 1969). Further study of these leucocyte antigens has been greatly facilitated by the development of a microlymphocytotoxicity technique (Terasaki and McClelland, 1964).

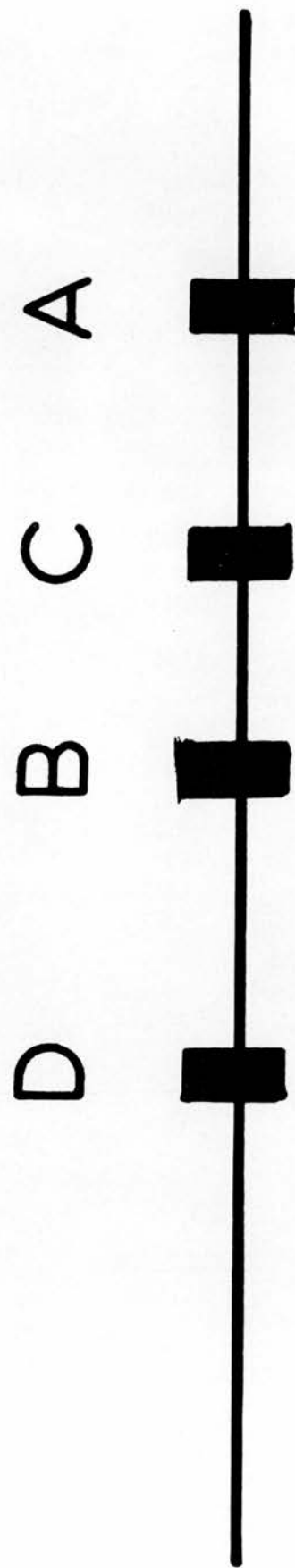
A third serologically defined locus has more recently been discovered (Sandberg et al, 1970) and this is now termed the HLA-C locus (WHO-IUIS Terminology Committee, 1975).

Demonstration that the genetic locus determining responsiveness in mixed lymphocyte cultures is in the same genetic region as the HLA-A and HLA-B loci came from studies of mixed lymphocyte culture responses between HLA-A and HLA-B identical siblings (Bach et al, 1967). The occurrence of positive mixed lymphocyte culture responses between some HLA-A and HLA-B identical siblings (Plate, Ward and Amos, 1970) demonstrated that this reaction defined a locus distinct from either of these serologically defined loci.

From these studies a genetic map of the major histocompatibility complex has been devised (Figure 2.1). The major histocompatibility complex has been assigned to autosome No.6 based on the demonstration of close linkage of this complex to the

Figure 2.1 Diagram to illustrate the arrangement of the four HLA loci, A, B, C and D of the major histocompatibility region.

fig. 2.1



locus for phosphoglucomutase (Lamm, Svejgaard and Kissmeyer-Nielsen, 1971) which itself has been assigned to this chromosome on the evidence of human-Chinese hamster somatic cell hybridisation (Jongsma et al, 1973). Further confirmation came from the study of a family with a pericentric inversion of chromosome No.6 (Lamm et al, 1974).

The WHO-IUIS Terminology Committee (1975) have reviewed and revised the nomenclature of the loci and their alleles which form the major histocompatibility complex. Their tabulated recommendations are given in Table 2.2. Certain specificities are provisional as they have not been fully defined by specific antisera in population and family studies by the Histocompatibility Workshops. These specificities have previously had the prefix W or been referred to by name or initials. The Terminology Committee on reviewing the data obtained at previous Histocompatibility Workshops have upgraded some of these to full HLA status (e.g. W27 is now HLA-B27). Others retain only workshop status and retain a W prefix to their number (e.g. W17 is now HLA-BW17). The numbering system has been revised so that if a specificity subsequently achieves full HLA status the W prefix can be dropped without also changing the number (e.g. W5 is now HLA-BW35 allowing the W to be dropped without confusion with the previous HL-A5 now HLA-B5).

Table 2.2 A complete listing of HLA specificities with revised nomenclature
(after WHO-IUIS Terminology Committee, 1975).

New	Old	New	Old	New	Old	New	Old
HLA-A1	HL-A1	HLA-AW32	W32	HLA-BW15	W15	HLA-CW1	T1
HLA-A2	HL-A2	HLA-AW33	W19.6	HLA-BW16	W16	HLA-CW2	T2
HLA-A3	HL-A3	HLA-AW34	Malay 2	HLA-BW17	W17	HLA-CW3	T3
HLA-A9	HL-A9	HLA-AW36	Mo	HLA-BW21	W21	HLA-CW4	T4
HLA-A10	HL-A10	HLA-AW43	BK	HLA-BW22	W22	HLA-CW5	T5
HLA-A11	HL-A11			HLA-BW35	W5		
HLA-A28	W28			HLA-BW37	TY		
HLA-A29	W29	HLA-B5	HL-A5	HLA-BW38	W16.1	HLA-DW1	LD 101
HLA-AW19	Li ^c	HLA-B7	HL-A7	HLA-BW39	W16.2	HLA-DW2	LD 102
HLA-AW23	W23	HLA-B8	HL-A8	HLA-BW40	W10	HLA-DW3	LD 103
HLA-AW24	W24	HLA-B12	HL-A12	HLA-BW41	Sabell	HLA-DW4	LD 104
HLA-AW25	W25	HLA-B13	HL-A13	HLA-BW42	MWA	HLA-DW5	LD 105
HLA-AW26	W26	HLA-B14	W14			HLA-DW6	LD 106
HLA-AW30	W30	HLA-B18	W18				
HLA-AW31	W31	HLA-B27	W27				

CHAPTER 3

PATIENTS AND METHODS

3.1 PATIENTS

A total of 360 patients were ascertained for this study. In addition to patients attending the rheumatology clinic at the Liverpool Royal Infirmary, patients were referred for this study by colleagues in the Merseyside and North Wales Region. All rheumatic patients were seen personally or by Dr. J. C. Woodrow. Each patient had a full clinical history taken, a full rheumatological examination and relevant laboratory investigation and radiographs to make a diagnosis of their current rheumatic disorder. They were then included in one of five diagnostic categories. No patients, other than two patients ascertained because of uveitis and found to have ulcerative colitis and ankylosing spondylitis, are included in more than one category.

3.1.1 Ankylosing Spondylitis

The New York criteria (Bennett and Wood, 1968) were used for the diagnosis of this condition in probands and relations. When adequate quality radiographs of the sacroiliac joints were available, they were used in the grading of sacroiliitis. When such radiographs were not available two views of the sacroiliac joints were obtained: an anteroposterior pelvic radiograph and a posteroanterior radiograph of the sacroiliac joints with a 15° downward caudal tilt.

Available radiographs of the sacroiliac joints were subsequently read at one sitting by two observers

(C. J. Eastmond and J. C. Woodrow), and an agreed grading recorded according to the New York criteria (Bennett and Wood, 1968). Examples are shown in Figures 3.1 - 3.5.

Available spinal radiographs were also viewed at the same sitting and the syndesmophytes present graded as marginal or non-marginal. A marginal syndesmophyte was considered present if it arose from the enthesis (Figure 3.6). A non-marginal syndesmophyte was considered present if it arose from the body of the vertebra leaving the enthesis uninvolved (Figure 3.7 (McEwan et al, 1973)). Osteophytes were distinguished from syndesmophytes by noting that they were initially lateral in projection from the vertebral body (Riley, Ansell and Bywaters, 1971).

3.1.2 Reiter's syndrome

The minimum criteria for this diagnosis in males were an arthritis occurring within a reasonable period of time of an episode of urethritis, or circinate balanitis (Csonka, 1958). In females an episode of urinary frequency or dysuria, or vaginitis associated with an arthritis were sufficient criteria.

Other features of the syndrome in its full form were noted.

An attempt was made to obtain radiographs of the sacroiliac joints (an anteroposterior pelvic radiograph

Figure 3.1 An example of radiologically normal
sacroiliac joints.



Figure 3.2 An example of grade 1 radiological
sacroiliitis.



Figure 3.3 An example of grade 2 radiological
sacroiliitis.

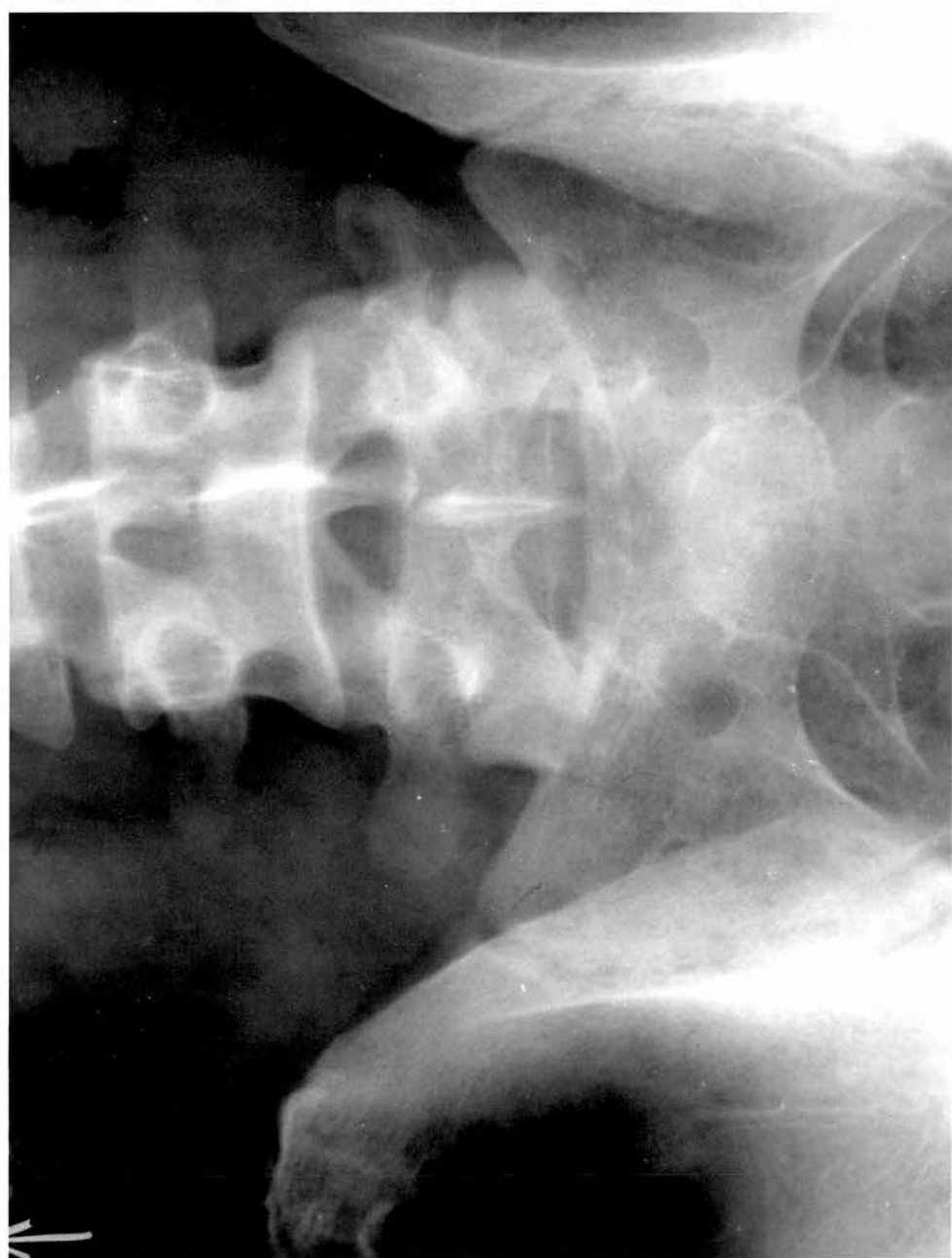


Figure 3.4 An example of grade 3 radiological
sacroiliitis.

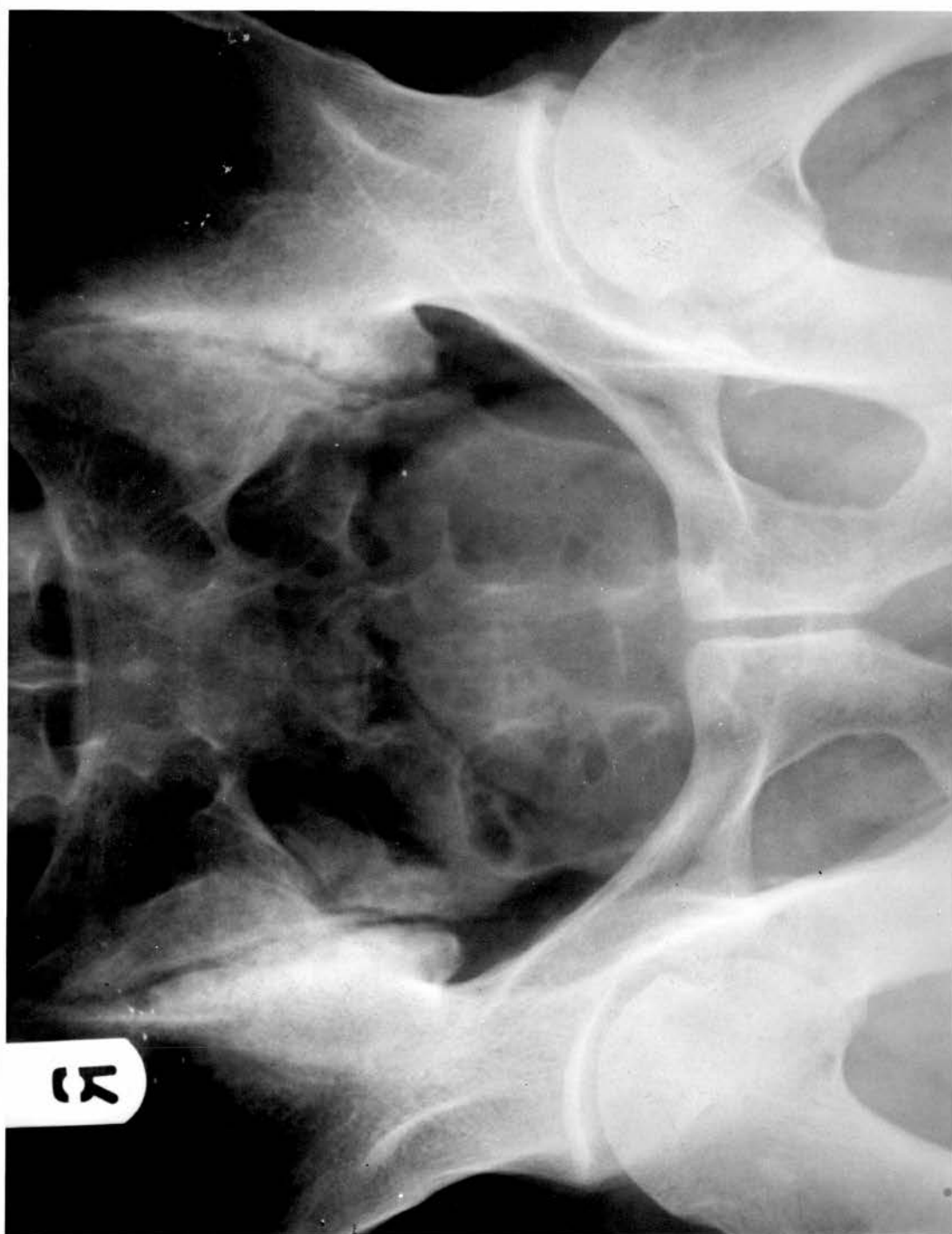


Figure 3.5 An example of grade 4 radiological
sacroiliitis.

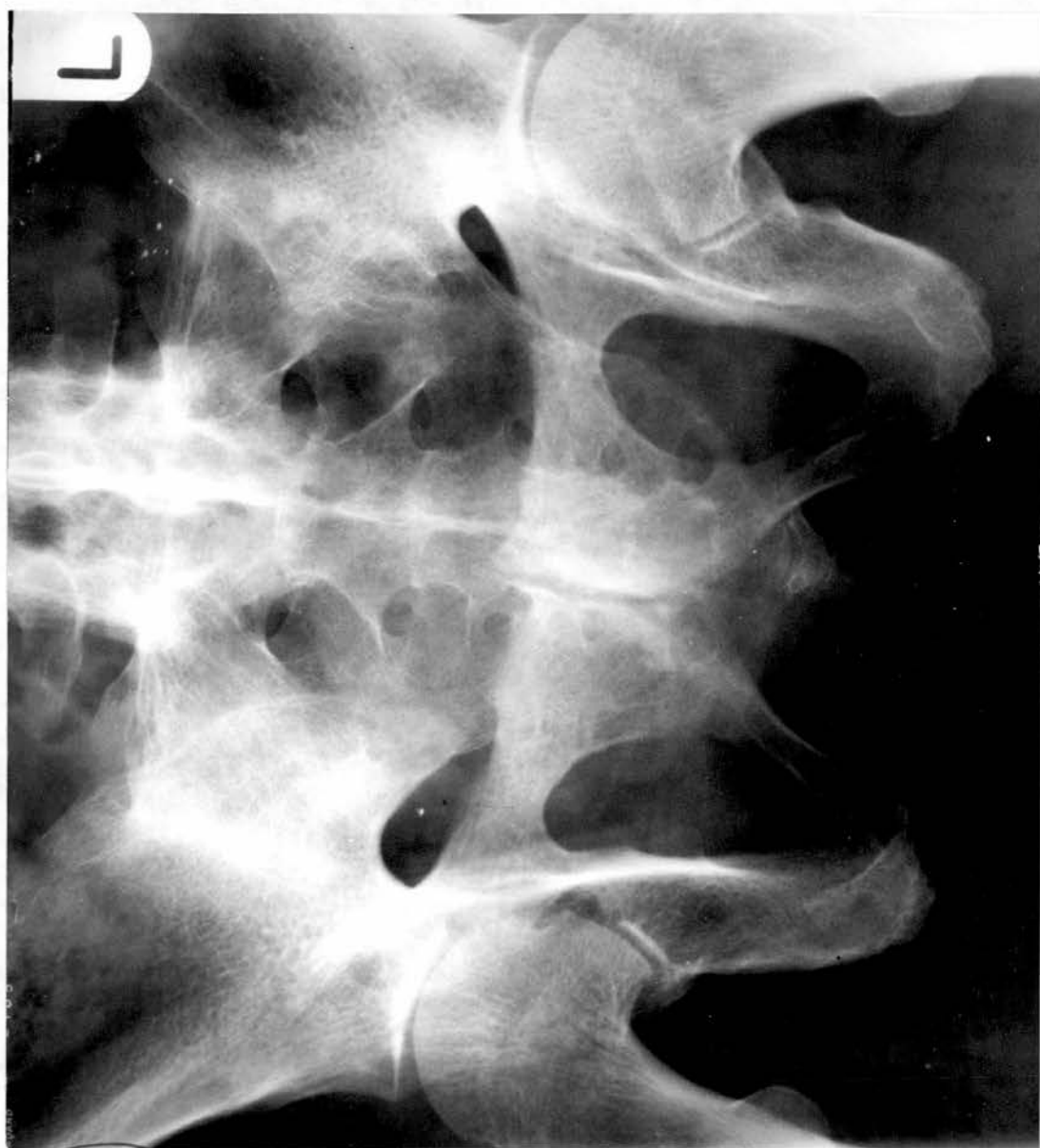


Figure 3.6 A radiograph showing a 'bamboo spine'
with marginal syndesmophytes.

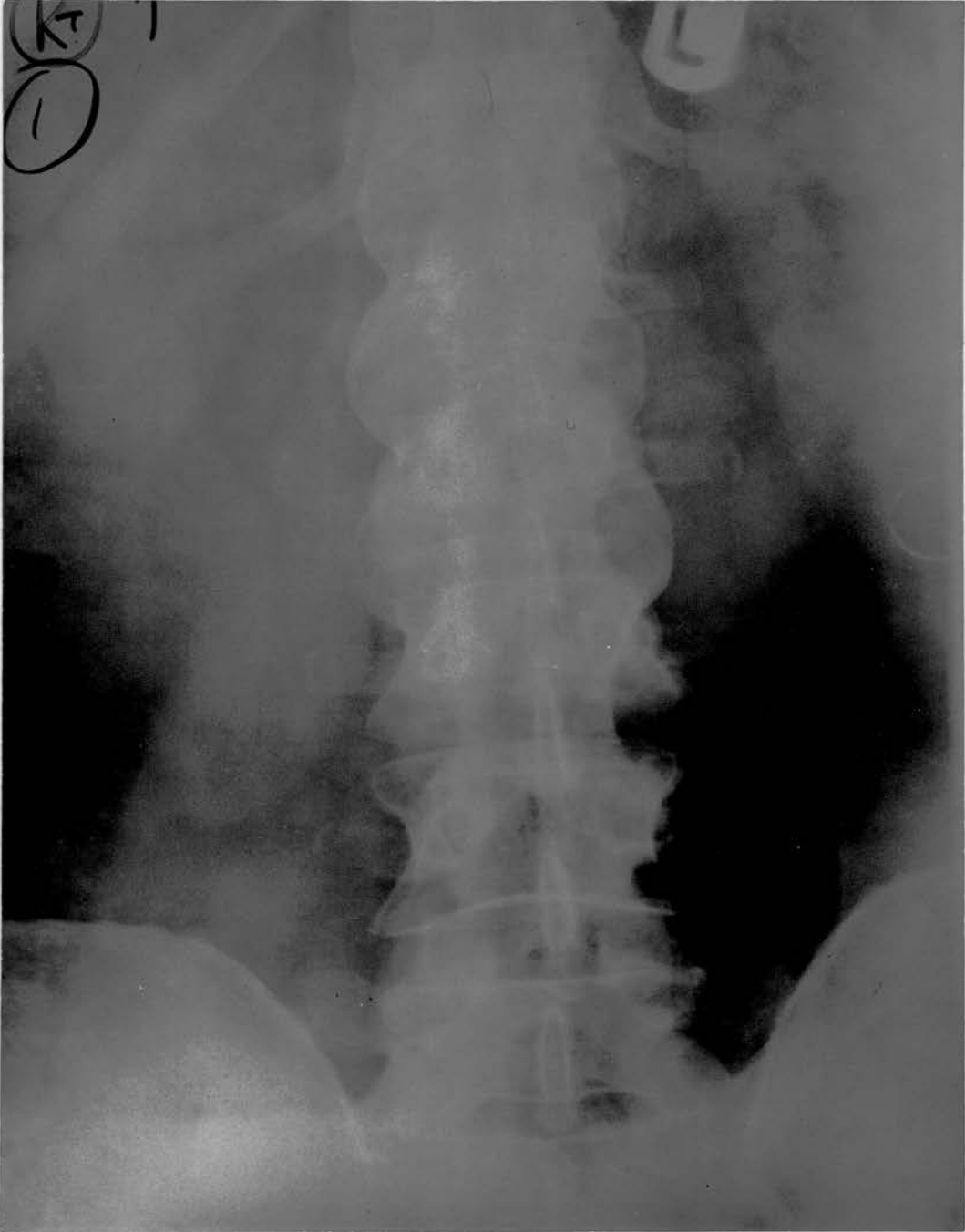


Figure 3.7 An example of a non-marginal
syndesmophyte.



and a posteroanterior sacroiliac joint radiograph) in all patients.

The first 50 patients were all seen by Dr. J. C. Woodrow and have been reported in detail elsewhere (Woodrow et al, 1974).

3.1.3 Psoriatic arthritis

The minimum criteria for inclusion in this group were an inflammatory arthritis of the peripheral joints or spine in a patient with psoriasis. Rheumatoid factor was tested for and titred in the serum of all patients using the sheep cell agglutination test.

Radiographs of relevant peripheral joints were obtained. All males and all females over the age of 45 years had radiographs of the sacroiliac joints (anteroposterior pelvic and posteroanterior pelvic radiographs).

Clinical, radiological and serological categorisation of the patients was performed at the completion of the study without regard to the results of the histocompatibility typing. These categories were determined in the light of our own experience of this disorder and coincide almost completely with those of Moll and Wright (1973(b)).

3.1.4 Chronic inflammatory bowel disease

The diagnosis of chronic inflammatory bowel disease had been established previously on the basis

of clinical symptoms and signs and typical abnormal bowel radiology, histology or operative findings by an experienced physician or surgical colleague. Patients known to have ankylosing spondylitis or in whom the diagnosis was symptomatically suggested were examined clinically and radiographs obtained of the sacroiliac joints (anteroposterior pelvis and posteroanterior sacroiliac joint radiographs).

The barium enema films of patients attending the specialist colon clinic at Liverpool Royal Infirmary were examined for abnormalities of the sacroiliac joints. Where these were suspected, whether symptoms were present or not radiographs of the sacroiliac joints were obtained as above.

The New York criteria for the diagnosis of ankylosing spondylitis (Bennett and Wood, 1968) were applied. When radiological sacroiliitis was present but there were insufficient clinical criteria for a diagnosis of ankylosing spondylitis then a diagnosis of radiological sacroiliitis alone was made.

3.1.5 Acute non-granulomatous uveitis

A histocompatibility antigen study of 90 patients (51 male, 39 female) with non-granulomatous anterior uveitis has been reported previously (Mapstone and Woodrow, 1975). All patients in whom rheumatic disorders or radiological abnormalities of the sacroiliac joints had been noted during that

study were recalled for further study. In addition 27 of the 63 patients with uveitis alone were chosen at random and a full clinical history obtained and a rheumatological examination made. The previously obtained radiographs of the sacroiliac joints were reviewed.

3.2 FAMILY STUDIES

3.2.1 Selected families

No attempt was made to ascertain all relatives of probands. When a proband gave a history of a diagnosed relevant condition in a relative, or when the proband's description of a relative's rheumatic complaints suggested a relevant condition, an attempt was made to see that relative. If the relative was willing, a full history, clinical examination and relevant radiographs were taken to establish the diagnosis according to the criteria applied to the probands. A blood sample was taken for histocompatibility testing. Where possible other members of these selected families were seen irrespective of the presence or absence of rheumatic complaints. A simple clinical history was taken. Blood was taken for histocompatibility testing in order to genotype the affected members of the family. If rheumatic complaints were present these were investigated further if the subject was willing.

In a few families the affected relatives did not live locally. Where possible diagnostic information

was obtained from their family practitioner or hospital consultant, and arrangements made to have the patient histocompatibility typed at a local centre. If no local facilities existed for histocompatibility typing, containers were sent to the family practitioner who, when he was willing, took the blood sample and returned it to us by express mail. Such samples were tested within 24 hours of being obtained.

3.2.2 Study of unselected parents

Where it was known that a proband with ankylosing spondylitis had both parents still living locally these parents were contacted. If they were willing a full clinical history was taken and rheumatological examination made. Irrespective of the clinical findings an anteroposterior radiograph of the pelvis and a posteroanterior radiograph of the sacroiliac joints with a 15° caudal tilt were taken. Blood was taken for histocompatibility typing. The radiographs were read by two readers (Drs. C. J. Eastmond and J. C. Woodrow) at one sitting without knowledge of the presence or absence of rheumatic complaints or abnormalities on clinical examination. They were graded for sacroiliitis according to the New York criteria (Bennett and Wood, 1968).

3.2.3 Study of identical twins

Monozygosity was confirmed by like sex and multiple red blood cell grouping.

A full clinical history was taken and rheumatological examination made of each twin. Radiographs of the sacroiliac joints were performed for each twin, and blood taken for histocompatibility antigen typing.

3.3 HISTOCOMPATIBILITY TESTING

X A modification of the microlymphocytotoxicity method described by Terasaki and McClelland (1964) was used. This modified test had been found previously to yield consistant and reliable results in our hands.

3.3.1 Blood samples obtained

10 mls of blood was obtained from each person by venepuncture. 4 mls were placed in a sterile glass tube containing 1 ml of a 0.6% solution of ethylenediaminetetra acetate (EDTA) in normal saline, and mixed thoroughly without shaking. The remaining 6 mls were placed in a sterile glass container without anticoagulant and allowed to clot.

3.3.2 Separation of lymphocytes

(a) Reagents

These were prepared in batches prior to use and stored.

Carbonyl iron powder mixture

10G of carbonyl iron powder

1 ml of 2,000 units/ml solution of heparin

5 mls of calcium chloride solution (40G in 2 litres)

and 10 mls of dextran solution.

Ficoll-Triosil mixture

130 mls of a 6.5% solution of Ficoll and one ampoule of Triosil were mixed together to a final specific gravity of 1.078.

Phosphate buffered saline

1.364G of potassium dihydrophosphate

1.425G of disodium hydrophosphate

15.250G of sodium chloride

These were made up to a final volume of 2 litres with distilled water.

(b) Preparation of lymphocyte suspension

4 mls of the EDTA anticoagulated blood were placed in a test tube and 4 mls of the carbonyl iron mixture added. The tube was stoppered and the contents mixed thoroughly. The tube was then placed in a water bath at 37°C, mixed twice at 10 minute intervals and then allowed to stand for a further 10 minutes at 37°C. If the cells had not completely settled after this period they were left longer, but not for more than a further 30 minutes.

X
Five parts of the supernatant from this tube were then carefully layered on to one part of the Ficoll-Triosil mixture in a centrifuge tube and centrifuged at 2,500 r.p.m. for 5 minutes.

thick layer
n
The layer of leucocytes was then removed into a clean tube and washed once with phosphate buffered saline. An aliquot of the cell suspension was transferred to a leucocyte counting slide, the cells counted and this suspension adjusted with phosphate

buffered saline to a final count of 2.0×10^9 lymphocytes per litre.

(c) Microlymphocytotoxicity test

Glass micro-test plates were prepared in batches. The wells were preformed by the use of printed circles on the glass plates using a silk screen technique. The plates were autoclaved. 2 μ l of each serum were inoculated into the wells according to a set plan (Figure 3.8). One plate each was used for sera to antigens of the A and B series respectively. These plates were then stored at -20°C until required.

After thawing liquid paraffin was poured over each plate to prevent drying, 2 μ l of the lymphocyte cell suspension was added to each well of both A and B plates, which were then incubated at 37°C for 30 minutes. 2 μ l of complement, prepared as three parts of pooled rabbit complement and one part of fresh human complement from AB Rhesus negative serum, were then added to each well and the plates incubated at 37°C for a further 30 minutes.

The excess serum was then removed from each well using a rotary pump to leave a layer of cells on the bottom of the well. 1 μ l of an 0.3% solution of Trypan blue in normal saline was added and the plates left standing at room temperature for 10 minutes. 1 μ l of 1% bovine albumin in saline and 1 μ l of 5% acetic acid in distilled water were then added to each well and the plates read using an inverted

Figure 3.8 An example of a histocompatibility
test plate for A and B series antisera.

microscope.

The percentage of cells killed was determined by counting the number of cells containing trypan blue per 100 cells, and the result for each well interpreted according to the scheme in Table 3.1. The whole test was performed within 24 hours of collecting the blood samples and usually in the afternoon of the day these were obtained. Samples were stored overnight, when necessary, at room temperature. This did not affect the results of the test and was especially convenient for samples obtained from relatives who were frequently visited at home in the evenings.

The serum from the clotted specimen obtained from each subject was tested for the ABO and rhesus red cell groups. The remaining serum was stored at -20°C in case of further use.

3.3.3 Controls for histocompatibility testing

These were blood donors and members of staff. These controls were tested using an identical technique as for the patients and relatives.

3.4 STATISTICAL METHODS

The statistical methods for analysing data on histocompatibility antigen and disease associations have been discussed by Svejgaard et al (1974). They conclude that Woolf's method (Woolf, 1955) of analysing such data has certain advantages. A major

Table 3.1 The interpretation of the percentage of cells killed in the microlymphocytotoxicity test.

Percentage of cells killed	Result
0 - 10	- definite negative
11 - 15	\pm probably negative
16 - 30	(+) possible positive
31 - 50	+ probably positive
51 - 100	++ definite positive

advantage is the ability to pool data from several sources, even when the particular antigen frequency varies between the source populations. The Yate's correlation for small numbers in the ordinary Chi squared test cannot be used when wishing to combine such data.

Woolf's method (Woolf, 1955) was devised for comparing ABO blood group frequencies in diseases and populations. In considering disease association with histocompatibility antigen Woolf's method calculates the relative risk (x) for individuals of having the disease if they have a given antigen compared with having the disease if they do not have that antigen. This is determined from the cross-product ratio $\frac{(ad)}{(bc)}$ of a 2 x 2 table (see Table 3.2). As Woolf (1955) comments this is a more useful statistic than the ratio of the frequency of the antigen in patients and controls $\frac{a(c + d)}{c(a + b)}$ having more relevance when considering an individual patient with a particular antigen.

When an antigen is absent in a group of patients ($a = 0$) or present in all of them ($b = 0$) then the Woolf relative risk is equal to 0 and infinity respectively. Haldane's (1955) modification of Woolf's method can be applied under these circumstances when the relative risk $x = \frac{(2a + 1)(2d + 1)}{(2b + 1)(2c + 1)}$.

Table 3.2 Calculation of the Woolf (1955) relative

$$\text{risk } x = \frac{(ad)}{(bc)}$$

	No. of individuals		
	with the antigen	without the antigen	Total
Patients with the disease.	a	b	a + b
Controls without the disease.	c	d	c + d
Total	a + c	b + d	a + b + c + d = n

$$x = \frac{ad}{bc}$$

$$y = \ln.x$$

$$V = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

$$w = \frac{1}{V}$$

$$\chi^2 = wy^2$$

$$\text{Haldane modification} = x = \frac{(2a + 1)(2d + 1)}{(2b + 1)(2c + 1)}$$

$$V = \frac{1}{(a + 1)} + \frac{1}{(b + 1)} + \frac{1}{(c + 1)} + \frac{1}{(d + 1)}$$

This modification can also be used for small numbers.

If the antigen frequency in patients and controls is the same the relative risk (x) will equal unity. When more frequent in patients it will exceed unity and when less frequent in patients it will be less than unity. To determine the probability of the relative risk deviating from unity its value is first converted into its natural logarithm y ($y = \ln.x$), which has a symmetrical and more normal distribution than the relative risk x.

The variance (V) of y is $\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$ or if Haldane's modification is used $V = \frac{1}{a+1} + \frac{1}{b+1} + \frac{1}{c+1} + \frac{1}{d+1}$

The weight (w) of y is $\frac{1}{V}$ and $\chi^2 = wy^2$ with one degree of freedom.

To pool estimates of the relative risk from more than one series, the weighted mean of the individual y's (Y) is given by $Y = \Sigma wy / \Sigma w$ and the standard deviation of Y by $1/\sqrt{\Sigma w}$.

When antigen frequencies differ between populations it is unwise to numerically add the series together to obtain Σa , Σb , Σc and Σd from which to calculate χ^2 (Woolf, 1955) as misleading values will be obtained. The Woolf method allows for such differences between populations so that the probability that Y differs from zero is given by $\chi^2 = \frac{(\Sigma wy)^2}{\Sigma w}$ with

one degree of freedom. Alternatively $\chi^2 = Y^2 \sum w$ with one degree of freedom. The significance of heterogeneity between the y values for each of i individual series is given by $\chi^2 = wy^2 - Y^2 \sum w$ with (i - 1) degrees of freedom.

Various modifications and refinements of Woolf's method have been suggested but Svejgaard et al (1974) consider that for general use Woolf's method (1955) will give satisfactory results, Haldane's modification (1955) being necessary when one cell in the 2 x 2 table is equal to zero or small numbers are present.

When calculating the significance of the frequency of one of several independent variables tested one has to take into consideration the number of variables tested. Just as 20 random samples from a given population will by chance show a difference in one of them at the 5% level so comparison of 20 independent variables between two random samples from the same population will result in a significant difference by chance for one variable at the 5% level. This is a built-in characteristic of the meaning of probability in statistics. With independent variables the error of ascribing such a deviation to factors other than chance can be allowed for by multiplying the individual p values by the number of variables tested (Grumet et al, 1971).

Histocompatibility antigens, however, being allelic characters occurring at two genetic loci are not totally independent variables. One cannot have an increased frequency of one of them without there being a decreased frequency of one or more of the remaining alleles occurring at that locus in the population studied. In addition some alleles at the HLA-A locus are in linkage disequilibrium with others at the HLA-B locus (e.g. HLA-A1 and B8). No satisfactory method has been devised to allow for the number of antigens tested and at the same time allow for their interrelationships with each other. Svejgaard et al (1974) suggest that when considering individual antigens then multiplication of the individual p value by the number of antigens tested should prove reasonably satisfactory. More careful analyses may be necessary when wishing to analyse several antigens at the same time. These are not applicable to the present study in view of the strong association between the group of diseases studied and one particular histocompatibility antigen.

In order to correct individual p values a precise numerical value for each p value needs to be obtained. A close approximation to p values obtained by Fisher-Irwin exact test is given by twice the p value obtained for the normal probability integral for χ of the corresponding χ^2 value for one

degree of freedom (Cudworth and Woodrow, 1976). This method has been used throughout in determining the exact p values for HLA antigen comparisons.

For each HLA antigen comparison between patients and controls the Yate's corrected Chi square (χ^2_c) has been calculated. Values of Woolf's (1955) relative risk (x), wy^2 and associated statistics have been calculated for each antigen tested.

In the combined analyses of antigen frequencies from several series the Haldane (1955) modification of Woolf's method has been used in view of the small numbers in some series.

CHAPTER 4

RESULTS

4.1 ANKYLOSING SPONDYLITIS

A total of 119 patients were seen who satisfied the New York diagnostic criteria for ankylosing spondylitis. One hundred and four were males and 15 were females. At the time of original ascertainment their average age was 40.8 years with a range of 16 to 73 years (Fig. 4.1). There was no difference in age between the sexes; the males average age was 40.8 years (range 16 to 73 years) and for females was 40.1 years (range 22 to 70 years).

4.1.1 Age of onset of ankylosing spondylitis (Fig. 4.2)

In 117 patients it was possible to determine from the history the age of onset of back symptoms with reasonable accuracy. Overall the mean age of onset was 25.6 years with a range of 10 to 60 years. Males and females did not differ in this respect. The mean age of onset in 102 males was 25.5 years (range 10 to 52 years) and in 15 females was 25.9 years (range 17 to 60 years).

4.1.2 Peripheral arthritis

A total of 46 (38.7%) patients were seen who had a peripheral arthritis at some point in time.

(a) Rheumatoid arthritis: one male was seen who, following the onset of his ankylosing spondylitis developed an erosive small joint peripheral arthritis indistinguishable from rheumatoid arthritis. He had subsequently developed a

Figure 4.1 Histogram of age by quinquennium at the time of ascertainment in males and females with ankylosing spondylitis.

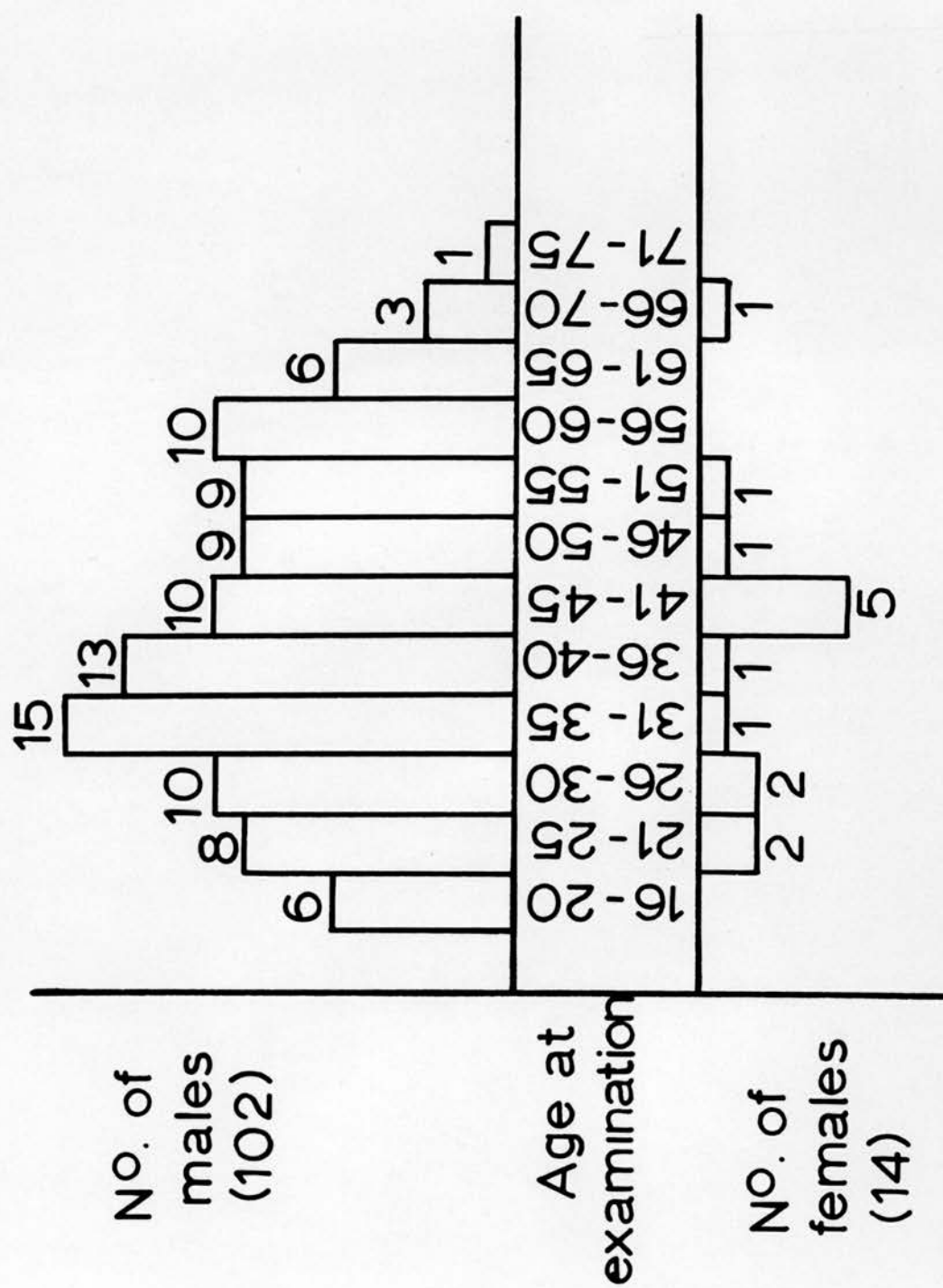


FIGURE 4.1.

Figure 4.2 Age of onset by quinquennium of
ankylosing spondylitis in males and
females.

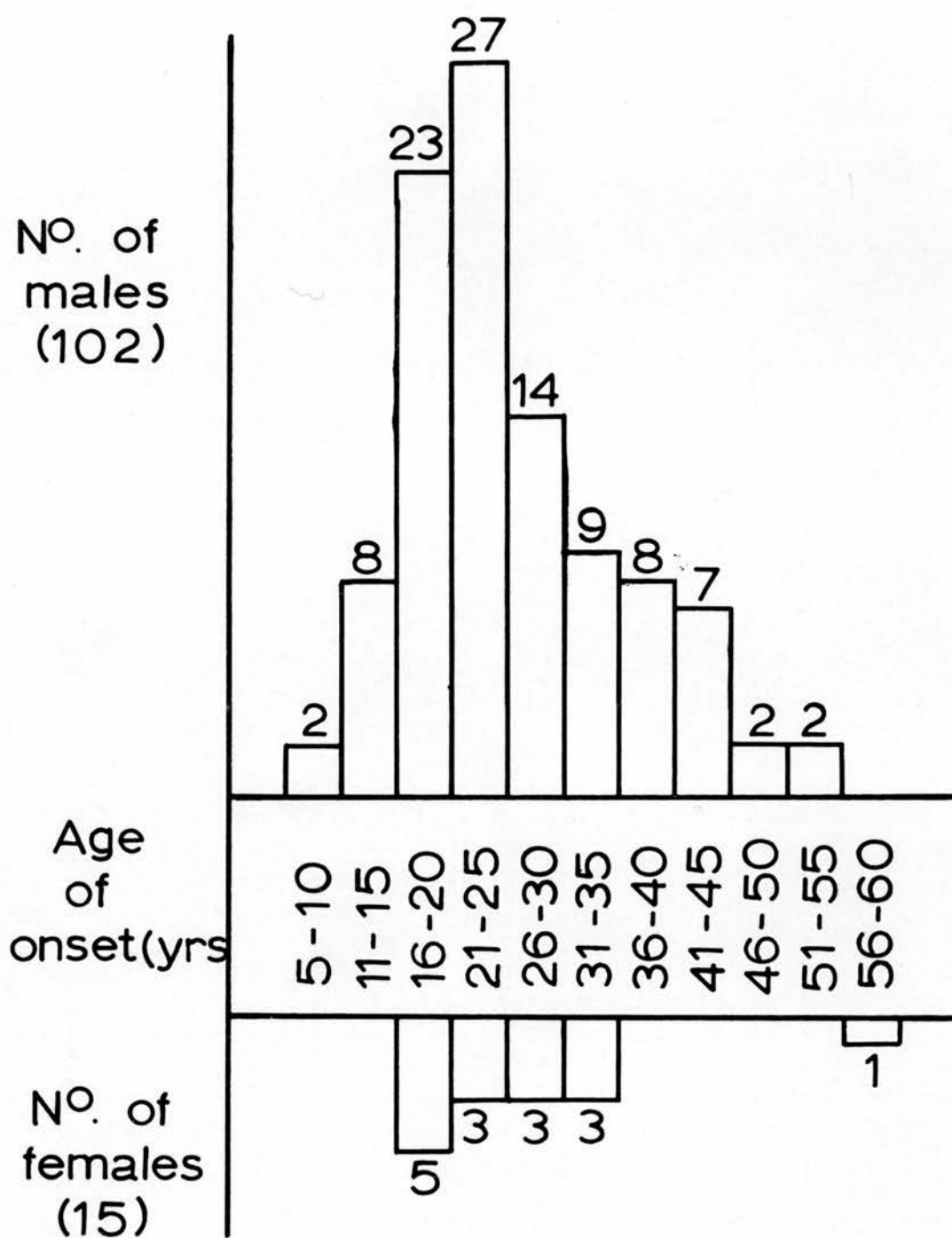


FIGURE 4.2.

nodule over the olecranon process which was excised and had the typical histology of a rheumatoid nodule. He was seropositive for rheumatoid factor.

(b) Reiter's syndrome: two male patients were seen who had a well documented episode of Reiter's syndrome. In both this had preceded the back symptoms, in one by six years and in the other by 10 years. In both there had been an asymptomatic interval between the resolution of the Reiter's syndrome and the onset of the back symptoms. Neither of them had any other episode of peripheral arthritis.

A 66 year old male with symptomatic onset of his ankylosing spondylitis at the age of 32 years developed, at the age of 62 years, an acute synovitis of the ankles, both wrists and the metacarpophalangeal joints of both hands simultaneous with a circinate balanitis, keratoderma blenorrhagica of the palms and soles, and a conjunctivitis but without dysuria, urethral discharge or diarrhoea. This episode resolved over a period of six to nine months without residua. He also suffered from chronic bronchitis necessitating hospital admission on several occasions.

(c) Peripheral arthritis preceding back symptoms: thirteen (10.9%) patients of whom 11 were male had a history suggesting an active synovitis of



peripheral joints before the commencement of their back symptoms. In all cases there was involvement of one or both knees (Table 4.1). In addition one male patient (Case 4.1(i)) also had swelling of the toes and symptoms of a plantar fasciitis. A further male had an inflammatory swelling of one elbow.

The mean age of onset of the peripheral arthritis in these 13 patients was 17.8 years (standard deviation = 5.8 years). The mean age of onset of their back symptoms was 23.8 years (standard deviation 9.5 years), which is not significantly different from the total series of 119 patients. The average delay between peripheral arthritis and back symptoms was 6 years, but there was a wide range from one to 25 years. In almost half the patients the back symptoms followed the peripheral arthritis within 3 years and in all except two patients within 10 years.

(d) Peripheral arthritis synchronous with back symptoms: four (3.4%) males had a virtually synchronous onset of a peripheral inflammatory arthritis and back symptoms, such that they were unable to describe which came first. In two the peripheral arthritis was limited to a knee and in two the peripheral arthritis involved the small joints of the hands and feet. One had an inflammatory swelling of the proximal inter-

Table 4.1 Peripheral arthritis preceding back symptoms
in 13 patients with ankylosing spondylitis.
Details of joints involved, age of onset of
peripheral arthritis and back symptoms, and
sex of patients.

	Peripheral joints affected	Age of onset of peripheral arthritis (yrs)	Age of onset of ankylosing spondylitis (yrs)	Difference in age of onset of peripheral arthritis and ankylosing spondylitis (yrs)	Sex of patient*
1	Left knee	12	19	7	M
2	Right knee, toes, heels	32	40	8	M
3	Knees	11	18	7	M
4	Knees	16	17	1	M
5	Elbow and right knee	16	23	7	M
6	Left knee	11	12	1	M
7	Knees	18	23	5	M
8	Knees	19	30	11	F
9	Knees	17	18	1	M
10	Knees	25	26	1	F
11	Knees	21	45	24	M
12	Knees	15	17	2	M
13	Left knee	18	21	3	M
Total	Knees 13 Toes 1 Heels 1 Elbow 1	231	309	78	M 11 F 2
Mean ages		17.8	23.8	6.0	

* M - Male
F - Female

phalangeal joints and "sausage" fingers (Case 4.1(ii)). The other had pain in the forefoot, and symptoms of an inflammatory arthritis in the hips (Case 4.1(iii)).

CX
(e) Peripheral arthritis succeeding back symptoms:
a total of 25 (21.0%) patients were seen who gave a history of an inflammatory peripheral arthritis occurring after the onset of back symptoms. One of these with a swollen proximal interphalangeal finger joint who had also had a synovitis of a knee one year prior to her back symptoms, was a female. One male gave an additional history of an inflammatory peripheral arthritis around the time he first noticed his back symptoms (Case 4.1(ii)). The knees, hips, wrists and toes were the most commonly involved joints in this group (Table 4.2).

In 16 patients it was possible from the history to determine with reasonable accuracy both the age of onset of back symptoms and peripheral arthritis. In these sixteen the mean age of onset of back symptoms was 22.3 years (range 10 to 53 years) and of the peripheral arthritis was 33.9 years (range 13 to 55 years) (Fig. 4.3), giving a mean difference of 11.6 years (range 1 to 35 years) (Fig. 4.4). The mean age of onset of back symptoms in these 16 did not differ significantly from that for the total series.

Table 4.2 Frequencies of involvement of individual peripheral joints in patients with ankylosing spondylitis, in whom the peripheral arthritis followed the back symptoms.

Peripheral joints involved	Males (104)		Females (15)		Total (119)	
	No.	%	No.	%	No.	%
<u>Lower limb</u>						
Hips	7	6.7	0	-	7	5.8
Knees	11	10.6	0	-	11	9.2
Ankles	1	1.0	0	-	1	0.8
Toes	4	3.8	0	-	4	3.4
Heels	2	1.9	0	-	2	1.7
<u>Upper limb</u>						
Shoulders	2	1.9	0	-	2	1.7
Elbows	2	1.9	0	-	2	1.7
Wrists	5	4.8	0	-	5	4.2
Proximal interphalangeal	1	1.0	1	6.7	2	1.7
<u>Others</u>						
Temperomandibular	1	1.0	0	-	1	0.8
Totals	24	23.1	1	6.7	25	21.0

Figure 4.3 Histogram of age of onset, by quinquennium, of the peripheral arthritis following the onset of ankylosing spondylitis in 16 patients.

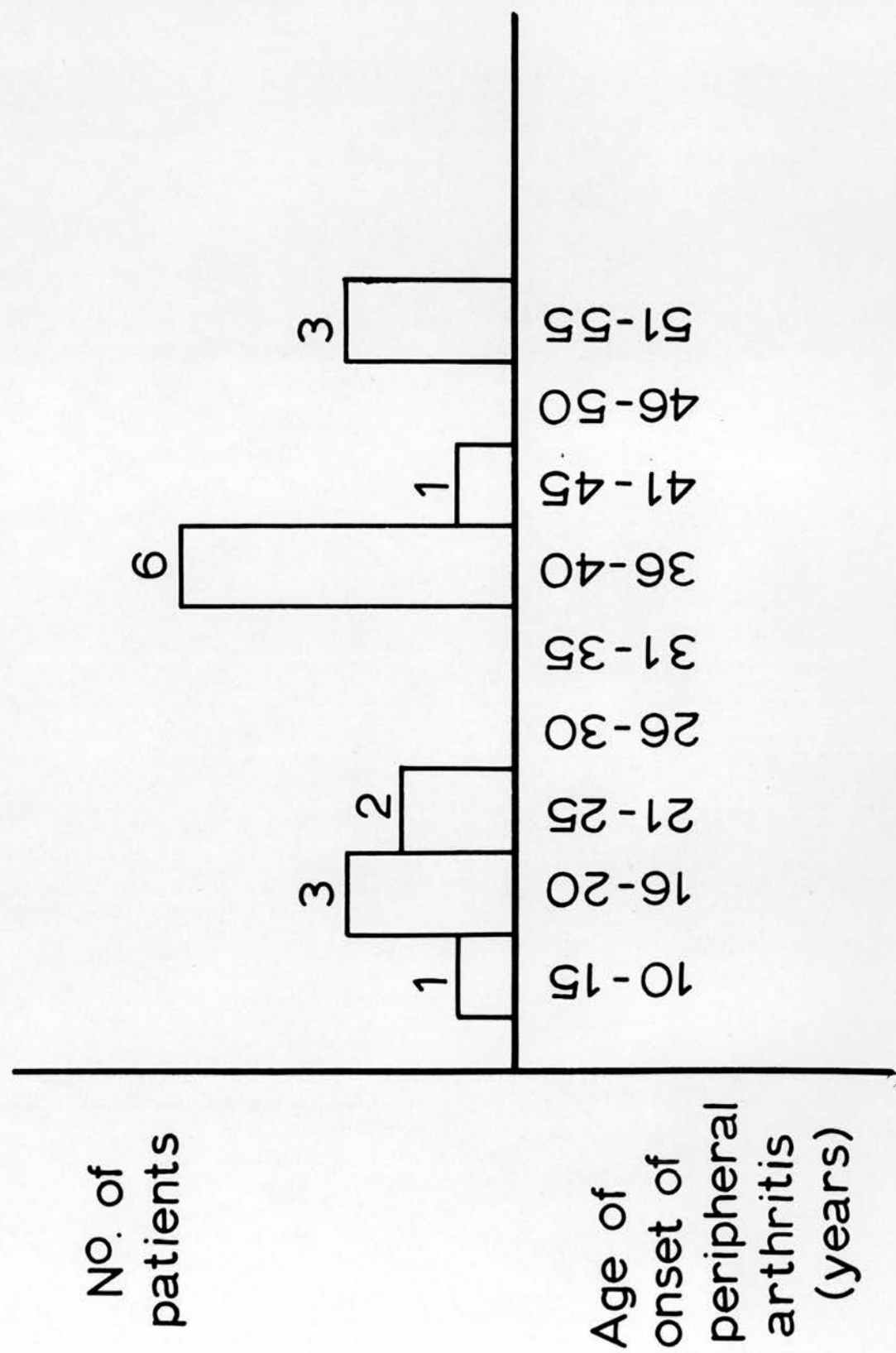


Figure 4.4 Histogram of duration of ankylosing
spondylitis before onset of
peripheral arthritis in
16 patients.

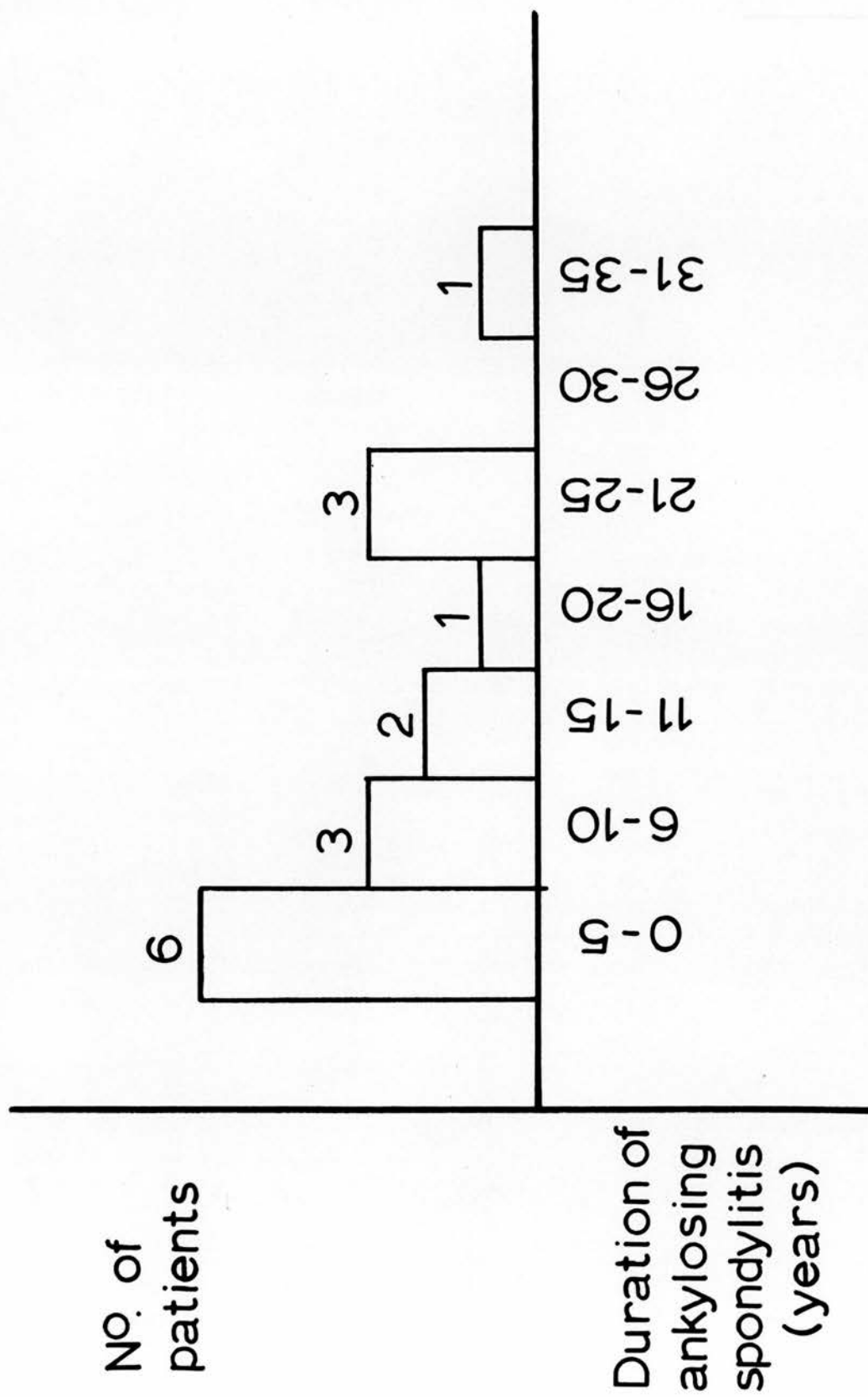


FIGURE 4.4.

4.1.3 Acute anterior uveitis

A total of 17 (14.3%) patients were seen who were known to have had an acute anterior uveitis or who gave a history strongly suggestive of this condition. Fourteen of these 17 were male and three were female. In nine males and two females, a total of 11 (64.7%), more than one episode of acute anterior uveitis had occurred.

4.1.4 Aortic Valve disease

One male patient (1.0% of males, 0.8% of all patients) was seen who had aortic incompetence who subsequently had a successful aortic valve replacement.

4.1.5 Apical pulmonary fibrosis

One proband was seen with this feature and an associated secondary aspergilloma from which he subsequently died.

4.1.6 Psoriasis

No patients with psoriasis of the skin at the time of original ascertainment were included in this group, but one, who ten years prior to the onset of his back symptoms gave a history of an inflammatory peripheral arthritis of the right knee and the right middle toe did develop a small patch of psoriasis on the front of the left knee one year after first being seen. He had had a nail dystrophy of a psoriatic type for ten years (Case 4.1(i)).

4.1.7 Radiology of the spine

Although radiographs of the sacroiliac joints were used to establish the diagnosis initially 109 were subsequently read again independent of the clinical details. Fifty-five showed bilateral grade 4 sacro-iliitis and two grade 4 on one side and grade 3 sacro-iliitis on the opposite side. Forty-seven showed bilateral grade 3 sacro-iliitis and five unilateral grade 3 with grade 2 sacro-iliitis on the opposite side. Five females had grade 4 bilateral sacro-iliitis and eight had grade 3 bilateral sacro-iliitis.

Seventy-eight patients had radiographs of the spine showing syndesmophytes. Seventy-two patients had only marginal syndesmophytes and two only non-marginal syndesmophytes. Four patients had examples of both types of syndesmophytes.

4.1.8 Family history

(a) Ankylosing spondylitis: ten patients (four females) gave a family history of an affected parent. All the affected parents were male apart from one mother. Twelve patients, all male, gave a history of an affected sibling. In ten instances this was a brother, in two a sister. One male had an affected son. Altogether twenty patients, four of whom were female, gave a history of one or more affected first degree relatives.

One male had a paternal uncle and father known to have ankylosing spondylitis and one female had a

paternal aunt and father with ankylosing spondylitis.

One male whose father also had ankylosing spondylitis had a cousin with ankylosing spondylitis and recurrent anterior uveitis (Pedigree P.10).

(b) Psoriasis: Three patients (one female) gave a history of psoriasis in a parent; in two instances the mother was affected and in one the father. Two patients (one female) had one or more siblings known to have psoriasis. In one instance it was a sister affected and in the other a brother and sister. One male had a son with psoriasis. Altogether four patients had a first degree relative known to have psoriasis. In two families more than one first degree relative was affected.

(c) Psoriatic arthritis: one male (Case 4.1(iv)) who himself had an arthritis suggestive of psoriatic arthritis but no psoriasis had a father with psoriatic peripheral arthritis.

(d) Chronic inflammatory bowel disease: one male had a mother with ulcerative colitis and a sister with ulcerative colitis and ankylosing spondylitis (Case 4.1(v)).

(e) Reiter's syndrome: one male who had a son with ankylosing spondylitis also had a niece with Reiter's syndrome (Pedigree P.14). The niece had been ascertained independently and it was through her that the family relationship was established.

(f) Twins: two patients had identical twin brothers and one patient had a father and uncle who were identical twins. These twins will be described in detail in Section 4.6.

4.1.9 Histocompatibility typing

All 119 patients were fully histocompatibility typed (Table 4.3). One hundred and four (87.4%) patients were found to be HLA-B27 positive, which is significantly more than the 37 of 451 controls (8.2%) found to be HLA-B27 positive ($\chi^2_c = 312.92$; $p = 5.4 \times 10^{-70}$). The only other histocompatibility antigen occurring with a significantly increased frequency was HLA-A2 which occurred in 74 (62.2%) of the patients and 197 (43.7%) of controls ($\chi^2_c = 11.80$; $p = 5.8 \times 10^{-4}$). This p value is still significant at the 2% level when multiplied by 25 to allow for the testing of 25 specificities. Twenty-one patients (17.7%) had only one B series antigen detected compared with 133 (29.5%) of the controls. Forty-three (36.1%) of the patients had only one A series antigen detected compared with 130 (28.8%) of the controls. Neither of these differences is statistically significant.

HLA-A1 occurred in only 19 patients (16.0%) compared with 154 (34.2%) of the controls ($\chi^2_c = 13.55$; $p = 2 \times 10^{-4}$). After multiplying by 25, the number of HLA specificities tested for $p = 0.005$. No other HLA antigen occurred with a significantly reduced frequency compared with controls.

Table 4.3 HLA frequencies in patients with ankylosing spondylitis and controls;
Yates χ^2 and Woolf relative risk and χ^2 (wy^2)

HLA antigens	Patients with ankylosing spondylitis (119)		Controls (451)		Yates χ^2	p	Relative risk \times	wy^2	p
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen					
A1	19	16.0	154	34.2	13.55	2×10^{-4}	0.366	13.91	1.9×10^{-4}
A2	74	62.2	197	43.7	11.80	5.8×10^{-4}	2.120	12.62	3.8×10^{-4}
A3	29	24.4	131	29.1	0.80	0.373	0.987	0.003	0.589
A9	17	14.3	88	19.5	1.38	0.242	0.688	1.70	0.194
A10	13	10.9	40	8.9	0.26	0.610	1.260	0.47	0.497
A11	15	12.6	58	12.9	0.01*	0.920	0.977	0.01	0.944
A28	7(118)	5.9	24(397)	6.1	0.00*	0.968	0.980	0.00	0.960
A29	4(110)	3.6	31(408)	7.6	1.52	0.219	0.459	2.06	0.150
AW30/31	4(92)	4.4	23(396)	5.8	0.10	0.795	0.737	0.30	0.582
AW32	9(98)	9.2	26(404)	6.4	0.50	0.478	1.470	0.44	0.342
A Blank	43	36.1	130	28.8	2.05	0.153	1.397	2.37	0.124
B5	2	1.7	44	9.8	7.22	0.007	0.119	8.51	0.004
B7	21	17.7	135	29.9	6.55	0.010	0.502	6.96	0.008
B8	18	15.1	128	28.4	8.00	0.005	0.450	8.36	0.004

Table 4.3 (Cont'd)

B12	21	17.7	128	28.4	5.08	0.024	0.541	5.21	0.023
B13	4	3.4	23	5.1	0.30	0.582	0.647	0.621	0.430
B14	4	3.4	33	7.3	1.82	0.177	0.441	2.19	0.139
BW15	10	8.4	45	10.0	0.12	0.726	0.828	0.27	0.603
BW16	0(28)	0	3(119)	2.5	2.58*	0.107	1.752	0.40	0.345
BW17	3	2.5	38	8.4	4.07	0.043	0.281	4.35	0.038
B18	5	4.2	25	5.5	0.12	0.726	0.747	0.34	0.562
BW22	4	3.4	25	5.5	0.53	0.465	0.593	0.91	0.343
B27	104	87.4	37	8.2	312.92	5.38×10^{-70}	77.578	179.10	7.92×10^{-41}
BW35	7	5.9	54	12.0	3.05	0.080	0.460	3.11	0.061
BW37	3(62)	4.8	5(141)	3.6	0.19*	0.660	1.383	0.20	0.667
BW40	11	9.2	51	11.3	0.23	0.631	0.799	0.41	0.522
B Blank	21	17.7	133	29.5	6.11	0.014	0.512	6.53	0.011

() Number of patients tested for each antigen

* Uncorrected χ^2 ; Yates correction would have resulted in an over correction
(i.e. $\frac{1}{2} (a + b + c + d) > (ad - bc)$)

(a) Sex: ninety of the 104 males (86.5%) and 14 of the 15 females (93.3%) were HLA-B27 positive. These two proportions do not differ significantly.

(b) Peripheral arthritis: of the 41 patients who gave a history of peripheral arthritis 37 (90.2%) were HLA-B27 positive, which is not significantly different from the series as a whole. The one male who also had nodular rheumatoid arthritis was HLA-B27 positive.

All 13 patients whose peripheral arthritis preceded the onset of their back symptoms were HLA-B27 positive.

Of the four patients with a synchronous onset of their peripheral arthritis and back symptoms two (50%) were HLA-B27 positive. The two HLA-B27 negative patients in this group both had a small joint arthritis of the fingers, including "sausage" fingers, or the forefoot (Cases 4.1(ii) and 4.1(iii) respectively).

Twenty-two of the 25 patients (88.0%) whose peripheral arthritis followed their back symptoms were HLA-B27 positive. This is not significantly different from the frequency of 87.2% found in the remaining 94 patients. The frequency of HLA-B27 was similar irrespective of the joint involved, apart from the toes where only one of the four patients (25.0%) with this type of peripheral joint involvement was HLA-B27 positive (Table 4.4). When compared with the remaining 21 patients with peripheral arthritis succeeding back symptoms, all of whom were HLA-B27

Table 4.4 Frequency of HLA-B27 related to individual joints involved in 25 patients whose peripheral arthritis followed the onset of back symptoms.

Peripheral joint involved	Number of patients with involvement	HLA-B27 positive	
		Number	Percent
<u>Lower limb</u>			
Hips	7	7	100.0
Knees	11	10	90.9
Ankles	1	1	100.0
Toes	4	1	25.0
Heels	2	1	50.0
<u>Upper limb</u>			
Shoulders	2	2	100.0
Elbows	2	2	100.0
Wrists	5	5	100.0
Proximal interphalangeal	2	2	100.0
<u>Others</u>			
Temperomandibular	1	1	100.0
Totals	25	22	88.0

positive then $\chi^2 = 17.12$ and $p = 3.5 \times 10^{-5}$.

In addition to these four patients, one HLA-B27 male had involvement of his toes prior to his back symptoms and later developed psoriasis (Case 4.1(i)). Therefore, overall five patients had toe involvement of whom 2 (40.0%) were HLA-B27 positive. When compared with a frequency of 91.8% HLA-B27 positive in the remaining 114 patients in the total series $\chi^2_c = 6.60$ and $p = 0.01$.

The two male patients with previously documented episodes of definite Reiter's syndrome were both HLA-B27 positive.

The 66 year old male with acute peripheral arthritis, circinate balanitis, keratoderma blenorrhagica and conjunctivitis 30 years after the onset of his ankylosing spondylitis was HLA-A2,11; B8, W35.

(c) Acute anterior uveitis: sixteen of the seventeen patients (94.1%) who had had acute anterior uveitis were HLA-B27 positive which is not significantly different from the 86.3% of the remaining 102 patients who did not have anterior uveitis. The one HLA-B27 negative patient was a male who had had one episode of acute anterior uveitis. All eleven patients with recurrent anterior uveitis were HLA-B27 positive.

(d) Aortic valve disease: the one male patient who had aortic incompetence was HLA-B27 positive.

(e) Apical fibrosis: the one male with this feature was HLA-B27 positive.

(f) Radiology of the spine: of the 109 patients whose sacroiliac joint radiographs were available for independent reading, 94 (86.2%) were HLA-B27 positive, which is similar to the total series. The proportion of patients with each grade of sacroiliitis did not differ with respect to the presence or absence of HLA-B27 (Table 4.5).

Sixty-nine of the 78 patients (88.5%) who had their spinal radiographs assessed for syndesmophytes were HLA-B27 positive, a frequency which is similar to the total series. All nine HLA-B27 negative patients had marginal syndesmophytes. The six patients who had non-marginal syndesmophytes, either alone or in combination with marginal syndesmophytes were HLA-B27 positive.

(g) Family history:

(i) ankylosing spondylitis: nineteen of the twenty probands who had a relative with ankylosing spondylitis were HLA-B27 positive. In all 15 instances where the affected relative was available they too were HLA-B27 positive. In the 13 families in which it was possible to determine the histocompatibility genotype the proband and affected relative had inherited the same histocompatibility haplotype.

There was one male who was HLA-B27 negative with a sister who also was HLA-B27 negative and

Table 4.5 HLA-B27 and the grading of sacroiliitis in 109 patients with ankylosing spondylitis

	Grade of sacroiliitis*				
	Grade 3 unilateral +2 contralateral side	Grade 3 bilateral	Grade 4 unilateral +3 contralateral side	Grade 4 bilateral	Total
Number HLA-B27 positive	49 (47.4)	1 (1.7)	39 (40.5)	5 (4.3)	94
Number HLA-B27 negative	6 (7.6)	1 (0.3)	8 (6.5)	0 (0.7)	15
Total	55	2	47	5	109

* grade of sacroiliitis using New York criteria

() figures in parentheses are the calculated expected in each cell

$\chi^2 = 3.48$ with 3 degrees of freedom $0.5 > P > 0.3$

had definite ankylosing spondylitis and ulcerative colitis (Case 4.1(v); Pedigree P.26). This family will be described in more detail in Section 4.6.2.

(ii) Psoriasis: all four patients with a first degree relative with psoriasis were HLA-B27 positive.

(iii) Psoriatic arthritis: the one male patient whose father had psoriatic peripheral arthritis was HLA-B27 negative (Case 4.1(iv); Pedigree P.16).

(iv) Chronic inflammatory bowel disease: the one male patient who had a strong family history of ulcerative colitis was HLA-B27 negative (Case 4.1(v); Pedigree P.26).

(v) Reiter's syndrome: the one male who had a niece with Reiter's syndrome was HLA-B27 positive. It was possible to genotype the affected members of this family and to demonstrate that they had inherited the same histocompatibility haplotype (Pedigree P.14).

(h) Age of onset of ankylosing spondylitis: the mean age of onset in the total series was 25.6 years. In the 102 HLA-B27 patients in whom the age onset could be determined from the history the mean age at onset was 24.5 ± 9.56 years (mean \pm s.d.) (Table 4.6). In the 15 HLA-B27 negative patients it was 31.1 ± 10.44 years (mean \pm s.d.). Calculating Student's t gives a value of 2.35 with 115 degrees of

Table 4.6 Mean age of onset and standard deviation in
HLA-B27 positive and negative males and
females with ankylosing spondylitis

		Number of patients	Mean age of onset (years)	Standard deviation (years)
HLA-B27 positive	Males	88	24.5	9.42
	Females	14	24.5	12.56
	All	102	24.5	9.56
HLA-B27 negative	Males	14	31.9	10.34
	Females	1	20.0	-
	All	15	31.1	10.44

freedom and $p < 0.02$. In males alone the mean age of onset in the 88 HLA-B27 positive males was 24.5 ± 9.42 years (mean \pm s.d.) and in the 14 HLA-B27 negative males was 31.9 ± 10.34 years (mean \pm s.d.). These give a Student's t value of 2.71 with 100 degrees of freedom and $p < 0.01$. The 14 HLA-B27 positive females had a mean age of onset of 24.5 ± 12.56 (mean \pm s.d.) which is the same as in HLA-B27 positive males.

(j) Histocompatibility typing of HLA-B27 negative patients: the only HLA specificities occurring with an increased frequency in the 15 HLA-B27 negative patients compared with the 104 HLA-B27 positive patients were HLA-BW35 and BW37 (Table 4.7). HLA-BW35 occurred in four of the fifteen (26.7%) HLA-B27 negative patients compared with three of the 104 (2.9%) HLA-B27 positive patients giving $\chi^2_c = 9.41$; $p = 0.002$ which multiplied by 24 to allow for the number of specificities tested for gives $p = 0.048$. HLA-BW37 occurred in three of the ten (33.3%) HLA-B27 negative patients and none of the 52 HLA-B27 positive patients tested for this histocompatibility type giving $\chi^2 = 16.55$; $p = 4.7 \times 10^{-5}$ which multiplied by 24 gives $p = 1.13 \times 10^{-3}$.

Compared with the 451 controls the χ^2_c for HLA-BW35 and HLA-BW37 in the HLA-B27 negative patients were 1.69 and 8.26 respectively (Table 4.7). Neither of these values is significant at the 5% level when allowance is made for the 24 specificities tested.

Table 4.7 HLA frequencies of other HLA antigens in HLA-B27 positive and negative patients with ankylosing spondylitis and in controls.

HLA antigens	[1] HLA-B27 negative patients with ankylosing spondylitis (15)		[2] HLA-B27 positive patients with ankylosing spondylitis (104)		[3] Controls (451)		Yates χ^2		
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen	[1] [2]	[1] [3]	[2] [3]
A1	3	20.0	16	15.4	154	34.2	0.01	0.74	13.13
A2	9	60.0	65	62.5	197	43.7	0.03*	0.98	11.27
A3	4	26.7	25	24.0	131	29.1	0.05*	0.04*	0.82
A9	4	26.7	13	12.5	88	19.5	1.14	0.13	2.34
A10	1	6.7	12	11.5	40	8.9	0.01	0.09*	0.35
A11	3	20.0	12	11.5	58	12.9	0.51	0.02	0.04
A28	0	-	7(103)	6.8	24(397)	6.1	1.10*	0.99*	0.00
A29	1	6.7	3(95)	3.2	31(408)	7.6	0.46*	0.02	1.69
A30/31	1(13)	7.7	3(79)	3.8	23(396)	5.8	0.41*	0.08*	0.16
AW32	1(14)	7.1	8(84)	9.5	26(404)	6.4	0.08*	0.01*	0.55
A blank	3	20.0	40	38.5	130	28.8	2.83	0.21	3.25
B5	0	-	2	1.9	44	9.8	0.30*	1.59*	5.83
B7	4	26.7	17	16.3	135	29.9	0.38	0.07*	5.88
B8	4	26.7	14	13.5	128	28.4	0.89	0.02*	9.11

Table 4.7 (Cont'd)

B12	3	20.0	18	17.3	128	28.4	0.07*	0.18	4.79
B13	1	6.7	3	2.9	23	5.1	0.58*	0.07	0.50
B14	0	-	4	3.8	33	7.3	0.59*	1.23*	1.13
BW15	3	20.0	7	6.7	45	10.0	1.51	0.68	0.70
BW16	0(5)	-	0(23)	-	3(119)	2.5	0.00	0.11*	0.61*
BW17	1	6.7	2	1.9	38	8.4	0.04	0.06*	4.45
B18	2	13.3	3	2.9	25	5.5	1.42	0.50	0.75
BW22	0	-	4	3.8	25	5.5	0.59*	0.87*	0.21
BW35	4	26.7	3	2.9	54	12.0	9.41	1.69	6.62
BW37	3(10)	33.3	0(52)	-	5(141)	3.6	16.55*	8.26	1.70
BW40	0	-	11	10.6	51	11.3	1.77*	1.80*	0.00
B blank	5	33.3	16	15.4	133	29.5	1.79	0.00	7.86

() Number of patients tested for each antigen

* Uncorrected χ^2 ; Yates correction would have resulted in an overcorrection (i.e. $\frac{1}{2} (a + b + c + d) > (ad - bc)$)

Individual Cases 4.1(i) - 4.1(v)

Case 4.1(i)

A 42 year old male gave a history of a sudden onset of upper lumbar, lower dorsal back pain with marked stiffness occurring two years previously. Subsequently he noticed back pain and stiffness in the mornings and after sitting and was restless at night owing to these symptoms. The onset of his backache had been preceded by redness of the right eye with blurring of the vision and was diagnosed as an acute anterior uveitis by an ophthalmologist. There had been one recurrence since.

Four years prior to the onset of his back symptoms he had had an episode of dysuria without discharge following extra marital sexual intercourse which he had been informed was non-specific urethritis.

At the age of 32 years he first noted pain under both heels and two years later his right knee became swollen for three weeks but continued to be intermittently painful. At the time of this synovitis he did not have any extra articular symptoms. Since the onset of his back symptoms these symptoms have continued with additional discomfort under the metatarsal heads and swelling of the right middle toe on one occasion for three weeks. Radiologically periostitis was noted in the proximal phalanx of this toe (Fig. 4.5).

About one year after first being seen he developed for the first time a small patch of psoriasis overlying the left knee. He had had onycholysis of the nails for over 10 years without other psoriatic features. At the time of the development of the skin lesion the nails became more markedly

Figure 4.5 Radiograph of the toes of the right foot of Case 4.1(i) showing periostitis of the shafts of the proximal phalanx of the middle toe.



involved. Nail clipping failed to grow any fungi.

His HLA typing was A2;B18,27.

This man illustrates the clinical overlap of ankylosing spondylitis and psoriatic arthritis. When he was first seen, in the absence of skin lesions he was included in the series of patients with uncomplicated ankylosing spondylitis, whereas subsequently he would have been placed in the psoriatic arthritis series. He also illustrates the occurrence of peripheral arthritis prior to the onset of the back symptoms.

Case 4.1(ii)

A 59 year old male who 24 years previously at the age of 35 years had a sudden onset of pain in the feet eased by exercise but repeatedly recurring after rest. Gradually these symptoms improved over the course of six to twelve months and as they did so he began to notice backache and stiffness most marked in the mornings. He had been treated with radiotherapy at that time with improvement in his back symptoms.

At the age of 42 years his back symptoms recurred. At the same time there was swelling of the whole of both long fingers (sausage digits) and some of the proximal interphalangeal joints of both hands. Over the subsequent years he has gradually developed swan-neck deformities of all fingers. He has also developed clawing of the toes of the left foot, but without any inflammatory joint swelling.

Two years before being seen, his right knee had been swollen for about two weeks. At no time did he have any dermatological, ophthalmological or urological complaints.

A sub-total thyroidectomy had been performed at the age of 28 years for primary thyrotoxicosis.

On examination, he had a slight kyphosis, a chest expansion of 2.5 cm and no lumbar spinal movement. There was marked restriction of the cervical spine. In the peripheral joints there were swan-neck deformities of all fingers and clawing of the toes of the left foot, the third toe having been amputated.

Radiologically his hands showed generalised osteoporosis and joint space narrowing of the metacarpophalangeal joints and both proximal and distal interphalangeal joints (Fig. 4.6). Radiographs of the sacroiliac joints showed a grade 4 sacro-iliitis.

He had no family history of relevant rheumatic disorders, nor of psoriasis or inflammatory bowel disease.

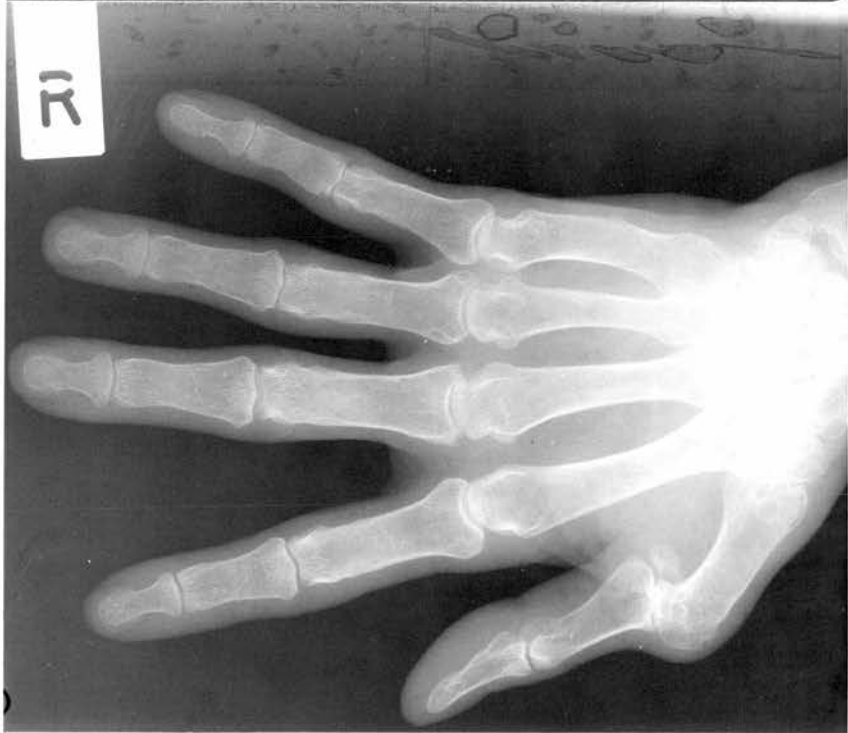
His HLA typing was A1,2;B8,W37.

This man illustrates a peripheral arthritis with features usually associated with psoriatic arthritis in a male with ankylosing spondylitis who is not HLA-B27. He also demonstrates the almost coincident onset of peripheral arthritis and back symptoms.

Case 4.1(iii)

A 36 year old male with ankylosing spondylitis and severe left hip disease for which replacement arthroplasty was performed gave a history that at the age of 28 years his left foot had become swollen and stiff for about three days. A fortnight later he developed pain and stiffness in the region of the left greater trochanter for which he received a period

Figure 4.6 Radiograph of the hands of Case 4.1(ii) showing generalised osteoporosis and joint space narrowing of both proximal and distal interphalangeal joints.



of four weeks bed rest without improvement. Gradually he noticed increasing low back and buttock stiffness most marked in the mornings on waking. During the first year of his rheumatic history he suffered a minor injury to the proximal interphalangeal joint of the right index finger, followed by gradual stiffening of this joint. A few weeks later, without further injury the distal interphalangeal joint of the right long finger became swollen and has remained swollen and stiff since that time. Radiologically there was erosive disease of these finger joints (Fig. 4.7).

He had noticed increasing left groin pain and difficulty in walking with pain. More recently his right knee had been stiff.

He had no eye symptoms at any time. At the age of 18 years he had a urethral discharge but no other symptoms at that time. There was no history of skin disease in himself or any member of his family. Close examination did not reveal any skin or nail lesions.

He had had some frequency of bowel action and rectal bleeding but not at the same time. Sigmoidoscopy and rectal biopsy were entirely normal.

His HLA typing was A2,10;BW15,18.

This patient demonstrates inflammatory arthritis in a distal interphalangeal finger joint in an HLA-B27 negative male with ankylosing spondylitis who did not have psoriasis of the skin or nails.

Case 4.1(iv)

A 25 year old male who at the age of 20 years first developed pain in the left buttock associated with morning

Figure 4.7 Radiograph of the right hand of Case 4.1(iii) showing erosive disease of the distal interphalangeal joint of the long finger and proximal interphalangeal joint of the index finger.



stiffness and causing him to limp. This gradually subsided over a period of two weeks only to recur one year later and has persisted ever since. At that time he first noticed pain under the metatarsal heads of the left foot and in the toes with some slight swelling of the toes. He has also had intermittent pain under the left heel eased by local steroid injections. There was no history to suggest conjunctivitis, uveitis, psoriasis, inflammatory bowel disease or urethritis.

On examination he had an erect posture with limitation of lumbar spinal extension. Forward flexion produced 6 cm skin distraction and lateral flexion 4 cm skin distraction. His chest expansion was 5 cm. The proximal interphalangeal joints of the second and third toes of the left foot were swollen, and there was tenderness of these joints as well as tenderness of the metacarpophalangeal and distal interphalangeal joints of these toes. He did not have psoriasis of skin or nail dystrophy.

Radiologically there was a grade 3 sacro-iliitis bilaterally. Radiographs of the left foot show erosions of the distal end of the proximal phalanx of the fifth toe (Fig. 4.8).

His HLA typing was A1,9;B7.

His 55 year old father gave a twelve year history of intermittent swelling and pain in peripheral joints lasting a few months at a time. The joints affected had been the proximal interphalangeal and metacarpophalangeal joints of the long and ring fingers of both hands, the elbows, knees and toes. He denied back symptoms. Eight years prior to being

Figure 4.8 Radiograph of the left foot of Case 4.1(iv) showing erosions of the distal end of the proximal phalanx of the fifth toe.



seen he had attended another hospital with pitting and onycholysis of the finger nails and a small patch of psoriasis on the elbows. He had occasionally had slight redness and grittiness of the eyes lasting a few days over a period of several years.

At the time he was seen personally he had good spinal movements in all directions, with good extension, forward flexion 6 cm skin distraction and lateral flexion 5 cm skin distraction. His chest expansion was 9 cm. He had a flexion deformity of the proximal interphalangeal joint of the right ring finger and some swelling without tenderness of the right ankle. His finger nails showed occasional nail pits and there were skin lesions suggestive of psoriasis on the extensor surfaces of the elbows and left knee.

Radiographs of his sacroiliac joints were entirely normal.

His HLA typing was HLA-A1,2;7,15 (Pedigree P.16).

There was no other known family history of psoriasis or arthritis.

This patient demonstrates a peripheral arthritis with features of psoriatic arthritis in a male patient with ankylosing spondylitis who was HLA-B27 negative, who also has a father with probable peripheral psoriatic arthritis but no evidence of ankylosing spondylitis or radiological sacroiliitis.

Case 4.1(v)

A 45 year old male gave a history that eight years previously he had suddenly, whilst sitting in a cinema, developed a pain in the right buttock radiating to the foot.

By the next morning he was asymptomatic. Subsequently he noticed aching in the right buttock radiating laterally. Similar but milder symptoms were noticed on the left. Two to three years later aching developed at the waist level, and was most marked in the morning on waking and during the night.

At the age of 25 years he had had an episode of renal colic. He had no other urinary symptoms, no eye, skin or bowel symptoms.

He stood with a mild kyphosis. On flexion his lumbar spine was flat, with reduction of all spinal movements. His chest expansion was 4 cm.

Radiographs of the sacroiliac joints showed a grade 3 bilateral sacroiliitis.

His sister aged 46 years first developed back pain and stiffness at the age of 28 years. She developed ulcerative colitis at 30 years and bronchial asthma at 41 years of age. Both these illnesses were well documented in the hospital case records.

When seen she had an erect posture, a chest expansion of 4.5 cm and restriction of all back movements. Forward flexion gave 6 cm, lateral flexion right and left 3 cm, skin distraction and extension 4 cm.

Radiographs of her sacroiliac joints showed a grade 3 bilateral sacroiliitis.

The proband's mother aged 71 years had had ulcerative colitis since the age of 26 years and had had a total colectomy. At the age of 68 years she had developed mid dorsal pain without stiffness. Over a five year period prior to being seen she had had some intermittent buttock aching and stiffness especially in the mornings.

She was very frail with a marked kyphosis, a chest expansion of 2 cm and limitation of all spinal movements. Forward flexion gave 2.5 cm, lateral flexion 1.5 cm bilaterally, skin distraction and extension 2 cm.

Radiographs of the spine showed marked osteoporosis. Those of the sacroiliac joints were difficult to interpret because of osteoporosis of the pelvis but were probably normal.

The proband's father was 77 years old and denied any rheumatic symptoms. He had normal spinal movements. No radiographs were taken. He was his wife's second cousin (Pedigree P.26).

The proband was HLA-A2.9; B7,W35. Other family members' HLA typings are shown in Pedigree P.26.

This patient demonstrates an HLA-B27 negative male with ankylosing spondylitis with a strong family history of ulcerative colitis.

4.2 ANKYLOSING SPONDYLITIS WITH CHRONIC INFLAMMATORY BOWEL DISEASE

A total of 13 patients were seen who had chronic inflammatory bowel disease and radiological sacroiliitis alone or clinical and radiological ankylosing spondylitis. Nine had ulcerative colitis (six males and three females) and four, all male, had Crohn's disease (Table 4.8).

4.2.1 Ulcerative colitis

(a) Age of onset

The mean age of onset of bowel symptoms in the nine patients with ulcerative colitis was 39.1 years (range 21 - 61 years). Asymptomatic grade 4 radiological sacroiliitis alone was present in two patients, one male and one female. One further female, who was also independently ascertained because of acute anterior uveitis, had limitation of all spinal movements, a chest expansion of 4 cm and radiological bilateral grade 2 sacroiliitis, but denied any rheumatic symptoms.

The remaining six patients had a mean age of onset of their back symptoms of 25.8 years (range 17 - 43 years). In five of these six patients the back symptoms preceded the onset of bowel symptoms by a mean of 9.8 years (range 3 - 25 years). In one male patient, originally ascertained because of recurrent anterior uveitis, the colitic symptoms preceded the rheumatic symptoms by two years.

Table 4.8 Numbers of patients with chronic inflammatory
bowel disease and ankylosing spondylitis or
radiological sacroiliitis alone.

Patients with		Ankylosing spondylitis	Radiological sacroiliitis alone	Total
Ulcerative colitis	Males	5	1	6
	Females	2	1	3
Crohn's disease	Males	4	0	4
	Females	0	0	0
Total		11	2	13

(b) Acute anterior uveitis

Four patients gave a history of acute anterior uveitis. In two patients, one male and one female, there had been several episodes, in one female two episodes had occurred and one male had had only one episode at the time of ascertainment. All had clinical ankylosing spondylitis.

(c) Psoriasis

No patient was seen who also had psoriasis.

(d) Family history

(i) Chronic inflammatory bowel disease.

No patient gave a history of a relative with either ulcerative colitis or Crohn's disease.

(ii) Ankylosing spondylitis.

Three male patients had a first degree relative with ankylosing spondylitis. One patient had a 50 year old father with a 19 year history of mild backache and stiffness, marked limitation of all spinal movements, a kyphosis, grade 4 radiological sacroiliitis and marginal syndesmophytes in the upper lumbar spine. The patient's mother was completely asymptomatic with normal spinal movements. Radiographs of her pelvis showed grade 3 bilateral sacroiliitis (Pedigree P.22). The patient's sister had psoriasis.

A further patient had a 64 year old father who gave a 30 year history of intermittent back pain without stiffness, normal spinal movements and

radiologically grade 4 sacroiliitis (Pedigree P.21). The patient's brother had psoriasis.

The third patient had a brother aged 52 years who at the age of 11 years had a brief episode of aching in the left buttock causing him to limp. Two years later he developed a swollen right knee which resolved spontaneously over a period of several months, but recurred two years later and was followed by pain under the heels and swelling of the right ankle. At 17 years of age he noticed that his back was becoming kyphotic and because of persistent buttock and groin pain was admitted to hospital. He was treated with bed rest and repeated manipulation being discharged over a year later with a completely rigid spine, hips and knees. On examination, no spinal movement was possible. He refused any radiological investigations. The patient's sister gave a history of two hospital documented episodes of acute anterior uveitis. She also had some occasional back pain and stiffness lasting a few days at a time. Her posture and spinal movements were normal. Radiographs of her back taken three years previously during an episode of acute anterior uveitis showed a bilateral grade 2 sacroiliitis. She refused any further radiological investigations (Pedigree P.25).

(iii) Psoriasis.

Three patients had a first degree relative with

psoriasis. Two of these three also had relatives with ankylosing spondylitis (vide supra - Pedigrees P.21 and P.22). A third female patient had a strong family history of psoriasis. Her 21 year old brother had psoriasis since 10 years of age. Her mother, aged 68 years, had psoriasis since 16 years of age and had three siblings, two deceased, with psoriasis. One of the patient's nephews, aged 18 years, had psoriasis for 11 years.

(iv) Acute anterior uveitis.

One male patient had a sister with a history of acute anterior uveitis and radiological grade 2 sacroiliitis (Pedigree P.25 vide supra).

4.2.2 Crohn's Disease

(a) Age of onset

The mean age of onset of abdominal symptoms in the four patients with Crohn's disease was 23.5 years (range 16 - 27 years). All four patients had clinical and radiological ankylosing spondylitis with a mean age of onset of back symptoms of 19.5 years (range 12 - 28 years).

Three of these four patients had back symptoms preceding their abdominal symptoms by a mean of 5.3 years (range 4 - 8 years). In the remaining patient the abdominal symptoms had preceded the back symptoms by one year.

(b) Acute anterior uveitis

One patient gave a history of recurrent acute anterior uveitis.

(c) Psoriasis

No patient was seen who also had psoriasis.

(d) Family history

(i) Chronic inflammatory bowel disease.

One patient had a younger brother aged 11 years with Crohn's disease. Their deceased father was known to have had ankylosing spondylitis (Pedigree P.23).

(ii) Ankylosing spondylitis.

Two patients had relatives known to have ankylosing spondylitis. One had a deceased father in whom the diagnosis had been well established and documented (vide supra Pedigree P.23). The other had a male cousin known to have ankylosing spondylitis whose mother had had several episodes of acute anterior uveitis and had a stiff back. Radiographs showed fused sacroiliac joints with syndesmophytes in her lumbar spine. Neither were seen personally as they lived in another part of the country (Pedigree P.24).

(iii) Psoriasis.

No relatives were known to have psoriasis.

(iv) Acute anterior uveitis.

A maternal aunt of one patient was known to have had acute anterior uveitis and also had a stiff

back and radiographs with the changes of ankylosing spondylitis (vide supra Pedigree P.23).

4.2.3 Histocompatibility Testing

Overall seven of the 13 patients (53.8%) were HLA-B27 positive which compared with a frequency of 8.2% in 451 controls, gives $\chi^2_c = 25.58$; $p = 2.1 \times 10^{-7}$ (Table 4.9). The frequency of HLA-B27 in the seven patients with ulcerative colitis and ankylosing spondylitis was 71.4%, in the four patients with Crohn's disease and ankylosing spondylitis 50.0%. Neither patient with ulcerative colitis and radiological sacroiliitis alone was HLA-B27 positive.

No other histocompatibility antigen occurred with a significantly increased or decreased frequency.

(a) Ulcerative colitis

(i) Age of onset and back symptoms.

Only one patient had back symptoms first developing after the age of 40 years. He was HLA-B27 positive.

In five patients their back symptoms preceded the onset of bowel symptoms. Four (80%) of these patients were HLA-B27 positive, compared with the one patient whose bowel symptoms preceded his back symptoms being HLA-B27 negative. Three patients had no back symptoms, two with radiological sacroiliitis alone were HLA-B27 negative, and one who had asymptomatic clinical ankylosing spondylitis was HLA-B27 positive.

Table 4.9 HLA frequencies in patients with chronic inflammatory bowel disease and ankylosing spondylitis or radiological sacroiliitis alone, and in controls.

HLA antigens	Patients with ulcerative colitis and ankylosing spondylitis (7)			Patients with Crohn's disease and ankylosing spondylitis (4)			All patients with chronic inflammatory bowel disease (13)			Controls (451)	
	Number with antigen	Percent with antigen	and radiological sacroiliitis alone (2)	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen
A1	0	0		0	0	2	50.0	2	15.4	154	34.1
A2	5	71.4		1	50.0	1	25.0	7	53.8	197	43.7
A3	3	42.9		0	0	1	25.0	4	30.8	131	29.0
A9	0	0		0	0	2	50.0	2	15.4	88	19.5
A10	1	14.3		0	0	0	0	1	7.7	40	8.9
A11	1	14.3		0	0	1	25.0	2	15.4	58	12.9
A28	3	42.9		0	0	0	0	3	23.1	24(397)	6.0
A29	0	0		1	50.0	0	0	1	7.7	31(408)	7.6
AW30/31	0	0		0	0	0	0	0	0	23(396)	5.8
AW32	0	0		1	50.0	0	0	1	7.7	26(404)	6.4
A blank	1	14.3		1	50.0	1	25.0	3	23.1	130	28.8
B5	1	14.3		0	0	1	25.0	2	15.4	44	9.8
B7	2	28.6		0	0	0	0	2	15.4	135	30.0

Table 4.9 (Cont'd)

B8	1	14.3	0	0	1	25.0	2	15.4	128	28.4
B12	2	28.6	2	100.0	1	25.0	5	38.5	128	28.4
B13	1	14.3	0	0	0	0	1	7.7	23	5.1
B14	0	0	0	0	0	0	0	0	33	7.3
BW15	1	14.3	0	0	1	25.0	2	15.4	45	10.0
BW16	0(0)	0	0(0)	0	0(1)	0	0(1)	0	3(119)	2.5
BW17	0	0	0	0	0	0	0	0	38	8.4
B18	0	0	0	0	1	25.0	1	7.7	25	5.5
BW22	0	0	0	0	1	25.0	1	7.7	25	5.5
B27	5	71.4	0	0	2	50.0	7	53.8	37	8.2
BW35	0	0	1	50.0	0	0	1	7.7	54	12.0
BW37	0	0	0	0	0	0	0	0	5(141)	3.6
BW40	0	0	1	50.0	0	0	1	7.7	51	11.3
B blank	1	14.3	0	0	0	0	1	7.7	133	29.5

() number of patients tested for each antigen

(ii) Acute anterior uveitis.

Of the four patients with a history of acute anterior uveitis, three (75%) were HLA-B27 positive compared with two of the remaining five patients (40%) who had not had uveitis.

(iii) Family history.

Of the three patients with a family history of ankylosing spondylitis two (66.6%) were HLA-B27 positive and in both these families the relative with ankylosing spondylitis had inherited the same HLA-B27 containing haplotype. The third proband, who was HLA-B27 negative had a HLA-B27 positive brother with ankylosing spondylitis alone, and one HLA-B27 negative sister with acute anterior uveitis and asymptomatic radiological grade 2 bilateral sacroiliitis. No HLA haplotype was inherited by all three siblings (Pedigree P.25).

All of the three patients who had first degree relatives with psoriasis were HLA-B27 positive.

(b) Crohn's Disease

(i) Age of onset.

No patient had an age of onset of back symptoms after 40 years. In three patients the back symptoms preceded the bowel symptoms and two of these (66.7%) were HLA-B27 positive. The one remaining patient whose bowel symptoms appeared first was HLA-B27 negative.

(ii) Acute anterior uveitis.

Only one patient had a past history of acute

anterior uveitis and he was HLA-B27 positive.

One of the three (33.3%) patients without uveitis was HLA-B27 positive.

(iii) Family history.

Both patients with a relative with ankylosing spondylitis were HLA-B27 positive and the affected relative had inherited the same HLA-B27 containing haplotype. The two patients without such a family history were HLA-B27 negative.

The one male with a younger brother with Crohn's disease alone was HLA-B27 positive, but his affected brother was HLA-B27 negative (Pedigree P.23).

(c) All chronic inflammatory bowel disease

Of the 10 patients who had back symptoms, in eight these had preceded the bowel symptoms. Six of these eight were HLA-B27 positive compared with both the two patients whose bowel symptoms came first being HLA-B27 negative. ($\chi^2 = 3.75$; $0.10 > p > 0.05$).

4.3 PSORIATIC ARTHRITIS

A total of 79 patients were seen who had both psoriasis and an inflammatory arthropathy. Forty-one (51.9%) were male and 38 female.

4.3.1 Classification of arthropathy

Five distinct groups of peripheral arthropathy were seen (Table 4.10). One of these could be further sub-divided into three sub-groups (Table 4.11).

Patients were classified as having a distal interphalangeal joint (DIP) arthritis if there had been a discrete inflammatory arthritis of one or more of these joints either as the sole manifestation or in association with a generalised arthritis. A total of 43 (22 male; 21 female) patients were seen with this type of arthritis.

The second group consisted of patients who had a polyarthrititis which did not satisfy the criteria for distal interphalangeal joint disease, nor did they have a symmetrical polyarthrititis of the rheumatoid type. This distinction was made on clinical or radiological criteria or both. The clinically distinguishing features found were marked asymmetry, dactylitis, and Achilles tendonitis. The radiological criteria was periarticular bone resorption (Figs. 4.9 and 4.10). A third sub-group of arthritis mutilans with telescoping digits was also recognised. This second group will be referred to as peripheral polyarthrititis for convenience. A total of ten patients clinically had this type of peripheral polyarthrititis; two

Figure 4.9 An example of periarticular bone
resorption in the distal ends of the
metatarsal bone producing a "whittled"
appearance.



Figure 4.10 An example of periarticular bone resorption in the distal end of a proximal phalanx of an index finger producing a "whittled" appearance.



Table 4.10 Diagnostic grouping of 79 patients with psoriasis and inflammatory arthritis.

Diagnostic group	Males		Females		Total
	Number	Percent	Number	Percent	
(1) DIP arthritis all " " alone " " with sacroiliitis " " sacroiliac joints not x-rayed	22 16 6 0	51.2 57.1 60.0 -	21 12 4 5	48.8 42.9 40.0 100.0	43 28 10 5
(2) Peripheral polyarthritis all " " alone " " with sacroiliitis	3 0 3	23.1 - 37.5	10 5 5	76.9 100.0 62.5	13 5 8
(3) Seronegative rheumatoid arthritis	2	50.0	2	50.0	4
(4) Seropositive rheumatoid arthritis	0	-	2	100.0	2
(5) Oligoarthritis all " " alone " " with sacroiliitis " " sacroiliac joints not x-rayed	6 2 4 0	85.7 100.0 100.0 -	1 0 0 1	14.3 - - 100.0	7 2 4 1
(6) Ankylosing spondylitis and radiological sacroiliitis all " " alone " " with peripheral arthritis	19 6 13	63.3 75.0 59.1	11 2 9	36.7 25.0 40.9	30 8 22
(7) Spondylitis without sacroiliitis all " " alone " " with peripheral " " arthritis	5 2 3	83.3 100.0 75.0	1 0 1	16.7 - 25.0	6 2 4
TOTAL	41	51.9	38	48.1	79

Table 4.11 Individual clinical, radiological and histocompatibility typing details of 13 patients with psoriasis and peripheral polyarthrititis (group 2)

Diagnostic sub-group	Sex (M/F)	Age (yrs)	Arthropathy							HLA typing	
			Clinical features			Radiological features					
			Asymmetry	Dactylitis		Achilles tendonitis	Peripheral joints	Sacroiliitis	A	B	
				fingers	toes						
Clinically distinguishable from rheumatoid arthritis	F	49	+	+	-	-	-	-	1	W17, 18	
	F	52	+	-	+	-	-	-	9, 28	14, W16	
	F	67	-	+	-	-	-	-	1, 3	8, 12	
	F	46	+	-	-	+	-	+	1, 2	13, 17	
	F	42	-	+	+	-	-	+	1, 3	27, W37	
	F	50	-	-	+	-	-	+	1, 10	12, W17	
	F	74	+	+	-	-	-	+	1, 2	7, 14	
	F	52	-	-	-	+	-	+	1, 2	12, 27	
	M	37	+	-	-	-	-	+	2	7, 12	
	F	31	+	-	-	-	-	-	2, 9	27	
Radiologically distinguishable from rheumatoid arthritis	F	59	-	-	-	-	-	+	3, 11	W17, W35	
	M	32	-	-	-	-	-	+	2, 10	12, 27	
Arthritis mutilans	M	73	-	-	-	-	-	+	3, 11	W16, W35	

M - Male; F - Female

patients had a symmetrical arthritis with distinguishing radiological features and one patient was seen with telescoping digits (Fig. 4.11) making a total in this group of 13 patients. Three of these 13 were male (Table 4.11).

The third and fourth groups consisted of six patients with a symmetrical polyarthritis indistinguishable clinically and radiologically from rheumatoid arthritis. Four (2 male; 2 female) were seronegative and form the third group and two (both females) were seropositive for rheumatoid factor and form the fourth group.

The final category of peripheral arthritis was that in which, when ascertained, only one joint other than a distal interphalangeal joint had been involved. This oligoarthritis had not persisted in any patient. In all cases the single joint involved was a knee. A total of seven patients (6 males; 1 female) were seen in this group.

A total of 30 patients were seen who had radiological sacroiliitis, with or without clinical ankylosing spondylitis. Of these 30, five had no back symptoms, and all these five also had a peripheral arthritis. A further 17 patients had classical ankylosing spondylitis and a peripheral arthritis, making a total of 22 patients (13 male; 9 female) with both peripheral arthritis and spinal disease. Ten of these 22 patients had distal interphalangeal joint disease, eight a peripheral polyarthritis and four an

Figure 4.11 Radiograph of the hands of a male patient with psoriatic arthritis mutilans resulting in telescoping digits.



Table 4.12 Diagnostic groups of peripheral arthritis
in 30 patients with ankylosing
spondylitis or radiological sacroiliitis
alone.

Peripheral arthritis group	Clinical and radiological ankylosing spondylitis	Radiological sacroiliitis alone
Distal interphalangeal joint arthritis	8	2
Peripheral polyarthritis	6	2
Oligoarthritis	3	1
None	8	0
TOTAL	25	5

oligoarthritis (Table 4.12). None of the six patients with symmetrical polyarthritis of the rheumatoid type had evidence of spinal disease, either clinically or radiologically. Six female patients (five with D.I.P. arthritis and one with oligoarthritis) did not have radiographs of the sacroiliac joints as they had no relevant symptoms and were under 45 years of age.

Eight patients were seen who had ankylosing spondylitis alone without any peripheral arthritis. Six of these eight were male.

Six patients were seen with the radiological appearances of syndesmophytes in the spine but without radiological sacroiliitis. Four of these six also had a peripheral arthritis, but two had spinal changes only.

4.3.2 Age

The mean age of the total group of 79 patients was 44.1 years (range 17 - 74 years). The mean age of the 38 females was 43.0 years and of the 41 males 45.1 years.

There were no significant differences in the mean age of patients in each diagnostic group although patients with radiological syndesmophytes without sacroiliitis tended to be older (mean age 61.0 years) than patients without (Table 4.13).

4.3.3 Psoriatic nail involvement

In 72 of the 79 patients the presence or absence

Table 4.13 Mean age at the time of examination of 79 patients with psoriasis and inflammatory arthritis with respect to diagnostic groups.

Diagnostic group		Total number of patients in each group	Mean age at examination (years)
(1) DIP arthritis all		43	44.8
" " alone		28	47.3
" " with sacroiliitis		10	47.7
" " sacroiliac joints not x-rayed		5	25.0
(2) Peripheral polyarthritis all		13	51.2
" " alone		5	51.8
" " with sacroiliitis		8	50.8
(3) Seronegative rheumatoid arthritis		4	42.3
(4) Seropositive rheumatoid arthritis		2	43.5
(5) Oligoarthritis all		7	47.3
" " alone		2	35.5
" " with sacroiliitis		4	60.3
" " sacroiliac joints not x-rayed		1	19.0
(6) Ankylosing spondylitis and radiological sacroiliitis all		30	47.0
" " alone		8	35.9
" " with peripheral arthritis		22	51.1
(7) Spondylitis without sacroiliitis all		6	61.0
" " alone		2	59.0
" " with peripheral arthritis		4	62.0
All patients		79	44.1

of nail involvement as evidenced by pitting, onycholysis, or horizontal ridging was noted (Table 4.14). The nails were involved in 39 (95.1%) of 41 patients with distal interphalangeal joint arthritis, in seven (58.3%) of 12 patients with peripheral polyarthritis and in three (60.0%) of five patients with oligoarthritis. In those patients with clinical ankylosing spondylitis or radiological sacroiliitis in these three groups the incidence of nail dystrophy was 100.0%, 75.0% and 100.0% respectively.

The nails were involved in one of the four patients with seronegative rheumatoid arthritis and in one of the two patients with seropositive rheumatoid arthritis.

Of 28 patients with ankylosing spondylitis or radiological sacroiliitis 23 (82.1%) had nail dystrophy, being present in 4 (57.1%) of seven patients without peripheral arthritis and 19 (90.5%) of 21 patients with peripheral arthritis.

Despite some differences in the frequency of nail involvement between different categories of arthropathy these differences are not statistically significant other than the higher frequency of nail dystrophy of 95.1% in 41 patients with distal interphalangeal joint arthritis compared with a frequency of 51.6% in the remaining 31 patients ($\chi^2_c = 16.2$; $p = 5.8 \times 10^{-5}$).

Table 4.14 Prevalence of nail involvement in 72 patients with psoriasis and inflammatory arthritis by diagnostic group.

Diagnostic group	Total Number	Nail involvement	
		Number	Percent
DIP arthritis all	41	39	95.1
" " with sacroiliitis	10	10	100.0
Peripheral polyarthritis all	12	7	58.3
" " with sacroiliitis	8	6	75.0
Seronegative rheumatoid arthritis	4	1	25.0
Seropositive rheumatoid arthritis	2	1	50.0
Oligoarthritis all	5	3	60.0
" " with sacroiliitis	3	3	100.0
Ankylosing spondylitis and radiological sacroiliitis all	28	23	82.1
" " with peripheral arthritis	21	19	90.5
" " alone	7	4	57.1
TOTAL	72	55	76.4

4.3.4 Uveitis

A total of six (7.6%) patients (3 male) gave a history of acute anterior uveitis. Of these four had ankylosing spondylitis, one (male) also having a history of a synovitis of a knee. A fifth patient (female) had a peripheral polyarthrititis alone, radiographs of the sacroiliac joints and spine being entirely normal. The sixth patient (female) had distal interphalangeal joint arthritis alone.

4.3.5 Family history

- (a) Psoriasis. Twenty-seven of the 74 patients gave a family history of psoriasis in a first or second degree relative. Of these 27 patients 11 (40.7%) were male and 16 (59.3%) female.
- (b) Psoriatic arthritis. One female patient with distal interphalangeal joint arthritis had an uncle with psoriatic peripheral arthropathy of a similar type (Pedigree P.32).
- (c) Ankylosing Spondylitis. Three patients (2 male) knew of a first degree relative with ankylosing spondylitis. In one instance the relative (a father) was deceased. In all instances the proband had ankylosing spondylitis, the one female also having a peripheral polyarthrititis.
- (d) Inflammatory bowel disease. One female patient with psoriasis and ankylosing spondylitis had a paternal aunt with ulcerative colitis (Pedigree P.33).

4.3.6 Histocompatibility Testing

The 79 patients were histocompatibility typed for 25 antigens (Table 4.15). Four antigens, HLA-A2, BW16, BW17 and B27 were present in significantly increased frequencies. HLA-A2 was present in 46 (58.2%) patients compared with 197 (43.7%) of 451 controls giving $\chi^2_c = 5.16$; $p = 0.023$. This p value, however, is not significant when allowance is made for the number of antigens tested ($p = 0.58$). HLA-BW16 was present in 4 (14.8%) of the 27 patients tested for this antigen, compared with three (2.4%) of the 119 controls tested giving $\chi^2_c = 4.84$; $p = 0.029$. This p value is not significant when allowance is made for the number of antigens tested ($p = 0.725$). HLA-BW17 was present in 21 (26.6%) of the 79 patients compared with 38 (8.4%) controls giving $\chi^2_c = 20.60$; $p = 5.6 \times 10^{-6}$. This p value is significant when allowance is made for the number of antigens tested ($p = 1.4 \times 10^{-4}$). HLA-B27 was present in 32 (40.5%) patients compared with 37 (8.2%) controls giving $\chi^2_c = 60.17$; $p = 8.8 \times 10^{-15}$. This p value remains significant when allowance is made for the number of antigens tested.

There was no increase in the frequency of HLA-B13 in the patients. Four (5.1%) patients were HLA-B13 positive compared with 23 (5.1%) controls.

(a) Sex. The frequencies of these HLA types was

Table 4.15 HLA frequencies in patients with psoriasis and an inflammatory arthropathy and in controls; Yates χ^2 and Woolf relative risk and χ^2 (wy^2), with their respective p values.

HLA antigens	Patients with psoriatic arthritis (79)		Controls (451)		Yates χ^2	p	Relative risk x	wy^2	p
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen					
A1	34	43.0	154	34.2	1.95	0.162	1.457	2.65	0.102
A2	46	58.2	197	43.7	5.16	0.023	1.797	5.62	0.018
A3	19	24.1	131	29.1	0.60	0.441	0.774	0.79	0.373
A9	11	13.9	88	19.5	1.04	0.317	0.667	1.37	0.242
A10	7	8.9	40	8.9	0.00	1.000	0.997	0.00	1.000
A11	9	11.4	58	12.9	0.03	0.857	0.871	0.13	0.719
A28	4(76)	5.3	24(397)	6.1	0.00	1.000	0.863	0.07	0.787
A29	2(76)	2.6	31(408)	7.6	1.77	0.184	0.329	2.25	0.134
A30/31	0(76)	-	23(396)	5.8	4.64	0.032	0.104	4.85	0.028
A32	1(76)	1.3	26(404)	6.4	2.27	0.131	0.194	2.55	0.114
A Blank	25	31.6	130	28.8	0.14	0.889	1.143	0.26	0.610
B5	6	7.6	44	9.8	0.16	0.689	0.760	0.37	0.542
B7	10	12.7	135	29.9	9.49	0.002	0.339	9.68	0.002
B8	10	12.7	128	28.4	7.83	0.005	0.366	8.06	0.005

Table 4.15 (Cont'd)

B12	20	25.3	128	28.4	0.18	0.674	0.855	0.32	0.575
B13	4	5.1	23	5.1	0.00	1.000	0.992	0.00	1.000
B14	6	7.6	33	7.3	0.00	1.000	1.041	0.01	0.928
BW15	5	6.3	45	10.0	0.66	0.412	0.610	1.03	0.313
BW16	4(27)	14.8	3(119)	2.5	4.84	0.029	6.725	5.72	0.017
BW17	21	26.6	38	8.4	20.60	5.6×10^{-6}	3.935	20.04	7.5×10^{-6}
B18	6	7.6	25	5.5	0.21	0.646	1.401	0.51	0.477
BW22	2	2.5	25	5.5	0.72	0.395	0.443	1.19	0.276
B27	32	40.5	37	8.2	60.17	8.8×10^{-15}	7.957	51.88	5.9×10^{-13}
BW35	5	6.3	54	12.0	1.63	0.201	0.497	2.08	0.150
BW37	2(76)	2.6	5(141)	3.6	0.13	0.719	0.735	0.13	0.719
BW40	10	12.7	51	11.3	0.02	0.873	1.137	0.121	0.726
B Blank	15	19.0	133	29.5	3.18	0.075	0.560	3.617	0.574

() numbers indicate number of persons tested for each antigen

similar in males and females. HLA-A2 was present in 26 (63.4%) males and 20 (52.6%) females; HLA-B16 in one (2.4%) male and three (7.9%) females; HLA-BW17 in 10 (24.4%) males and 11 (28.9%) females and HLA-B27 in 17 (41.5%) males and 15 (39.5%) females.

- (b) Classification of arthropathy. Table 4.16 gives the frequencies of HLA-BW17 and B27 in each diagnostic group of psoriatic arthritis. HLA-BW17 is present with an increased frequency in all groups of peripheral arthritis, but not in patients with ankylosing spondylitis or radiological sacroiliitis. Only 2 (6.7%) of these 30 patients were HLA-BW17 positive compared with 19 (38.8%) of the remaining 49 patients which gives $\chi^2_c = 8.23$; $p = 0.004$). HLA-BW17 was absent in the eight patients with ankylosing spondylitis without peripheral arthritis.

(i) Spinal arthritis

HLA-B27 occurred with an increased frequency in all diagnostic groups other than in patients with spinal syndesmophytes without radiological sacroiliitis in whom this antigen was absent. Twenty (66.7%) of the 30 patients with ankylosing spondylitis or radiological sacroiliitis were HLA-B27 positive which compared with the control frequency of 8.2% gives $\chi^2_c = 86.51$; $p = 1.4 \times 10^{-20}$, and with 11 (26.8%) of the

Table 4.16 Frequencies of HLA-BW17 and HLA-B27 with regard to diagnostic groups in 74 patients with inflammatory arthritis and psoriasis and radiographs of the sacroiliac joints and also in 451 controls.

Diagnostic group	Total	HLA-BW17		HLA-B27	
		Number	Percent	Number	Percent
(1) Distal interphalangeal arthritis all " " alone " " with sacroiliitis	43 28 10	14 11 1	32.6 39.3 10.0	15 8 6	34.9 28.6 60.0
(2) Peripheral polyarthritis all " " alone " " with sacroiliitis	13 5 8	3 2 1	23.1 40.0 12.5	5 1 4	38.5 20.0 50.0
(3) Seronegative rheumatoid arthritis	4	1	25.0	1	25.0
(4) Seropositive rheumatoid arthritis	2	1	50.0	1	50.0
(5) Oligoarthritis all " " alone " " with sacroiliitis	7 2 4	1 0 0	14.3 - -	2 0 2	28.6 - 50.0
(6) Ankylosing spondylitis and radiological sacroiliitis all " " alone " " with peripheral arthritis	30 8 22	2 0 2	6.7 - 9.1	20 8 12	66.7 100.0 54.5
(7) Spondylitis without sacroiliitis all	6	2	66.7	0	-
TOTAL	74	21	28.4	32	43.2
CONTROLS	451	38	8.4	37	8.2

41 patients with peripheral arthritis alone gives $\chi^2_c = 9.59$; $p = 0.002$.

All eight patients with psoriasis and ankylosing spondylitis alone were HLA-B27 positive. Twelve (54.5%) of the 22 patients with peripheral arthritis and ankylosing spondylitis or radiological sacroiliitis alone were HLA-B27 positive which is significantly less than the 100% frequency in the eight patients with psoriasis and ankylosing spondylitis alone ($\chi^2_c = 5.57$; $p = 0.018$), and also significantly less than the frequency of 87.4% in 119 patients with ankylosing spondylitis without psoriasis (Section 4.1) ($\chi^2_c = 11.56$; $p = 6.7 \times 10^{-4}$).

(ii) Peripheral arthritis

Ten (25.6%) of the 39 patients with seronegative peripheral arthritis alone were HLA-B27 positive which compared with a frequency of 8.2% in 451 controls gives $\chi^2_c = 10.66$; $p = 1.1 \times 10^{-3}$.

Fifteen (34.9%) of the 43 patients with distal interphalangeal joint arthritis were HLA-B27 positive. Comparison with a frequency of 8.2% in 451 controls gives $\chi^2_c = 26.90$; $p = 1.05 \times 10^{-7}$. Eight (28.6%) of the 28 patients in this group having radiologically normal sacroliac joints were HLA-B27 positive and comparison with the same controls gives

$\chi^2_c = 10.56$; $p = 0.0016$. Five (38.5%) of the 13 patients with peripheral polyarthritides were HLA-B27 positive which compared with 37 (8.2%) in 451 controls gives $\chi^2_c = 10.62$; $p = 0.0011$. The small numbers in each of the three sub-groups of this group preclude valid separate statistical analysis as does the small number of patients with radiologically normal sacroiliac joints.

- (c) Nail involvement. Sixteen (29.1%) of the 55 patients with nail involvement were HLA-BW17 positive compared with three (17.6%) of the seventeen patients without nail involvement giving $\chi^2_c = 0.39$; $0.7 > p > 0.5$. In the same 72 patients 23 (41.8%) of the 55 with nail involvement were HLA-B27 positive compared with eight (47.1%) of the seventeen without nail involvement giving $\chi^2_c = 0.01$; $0.8 > p > 0.4$.
- (d) Acute anterior uveitis. Five of the six patients with a history of acute anterior uveitis were HLA-B27 positive, and none were HLA-BW17 positive.
- (e) Family studies.

(i) Psoriasis.

Ten (37.0%) of the 27 patients with a known family history of psoriasis were HLA-BW17 positive compared with 11 (21.2%) of the 52 without such a family history ($\chi^2_c = 1.55$; $0.3 > p > 0.2$). Of the same 27 patients with a family history of

psoriasis 10 (37.0%) were HLA-B27 positive compared with 22 (42.3%) of the 52 patients without such a family history ($\chi^2_c = 0.04$; $0.9 > p > 0.8$).

(ii) Ankylosing spondylitis.

All three patients with a known family history of ankylosing spondylitis were HLA-B27 positive. None were HLA-BW17 positive. One of these patients (Pedigree P.15) was a male with psoriasis and ankylosing spondylitis alone whose father had ankylosing spondylitis and apical pulmonary fibrosis and was also HLA-B27 positive. Genotyping showed that the proband had inherited the gene for HLA-B27 from his father. The proband's mother had psoriasis, but was not available for personal study. A female aged 52 with psoriatic polyarthrititis and ankylosing spondylitis had a brother with ankylosing spondylitis alone. They were both HLA-B27 positive but genotyping was not possible in this family due to a lack of available relatives. The final patient's affected father was deceased.

(iii) Peripheral psoriatic arthritis.

An 18 year old girl with distal interphalangeal arthritis who was HLA-B27 positive had a paternal uncle with a similar arthritis and psoriasis who was also HLA-B27 positive. Genotyping demonstrated that they had not inherited

the same HLA-B27 positive haplotype but that both HLA-B27 positive haplotypes had probably come from a common ancestor (Pedigree P.32).

(iv) Inflammatory bowel disease.

A 25 year old female patient with psoriasis and ankylosing spondylitis alone who was HLA-B27 positive had a paternal aunt known to have ulcerative colitis. The HLA-B27 positive haplotype of the proband had been inherited from her mother. The proband's sister and father had psoriasis (Pedigree P.33).

4.4 REITER'S SYNDROME

A total of 77 patients were seen in whom Reiter's syndrome was diagnosed as the primary disease. The first 50 of these patients were not seen personally and have been reported elsewhere (Woodrow et al, 1974). Of the subsequent 27 patients 22 were seen personally and will be described in detail. The remaining five patients were seen only by Dr. J. C. Woodrow.

4.4.1 Details of 22 patients seen personally

Only one female was seen in these 22 patients, one other female having been seen in the previous 50 patients. The mean age of the 22 patients was 28.3 years and their age distribution is shown in Figure 4.12. Each five year age group from 16 to 40 years was equally represented.

(a) Urethritis and mucocutaneous lesions

All but two males were seen during the episode of acute Reiter's syndrome, and all but one, who had circinate balanitis, had subjective and objective evidence of a urethritis preceding the onset of arthritis. The one female had dysuria and frequency of micturition. Of the two males not seen during the acute attack one described a previous typical acute arthritis with urethritis (Case 4.4(i)) and the other had a well documented acute Reiter's syndrome with urethritis three years before (Case 4.4(ii)). The onset of the arthritis occurred within one week of the onset

Figure 4.12 Age distribution of 22 patients with
Reiter's syndrome seen personally.

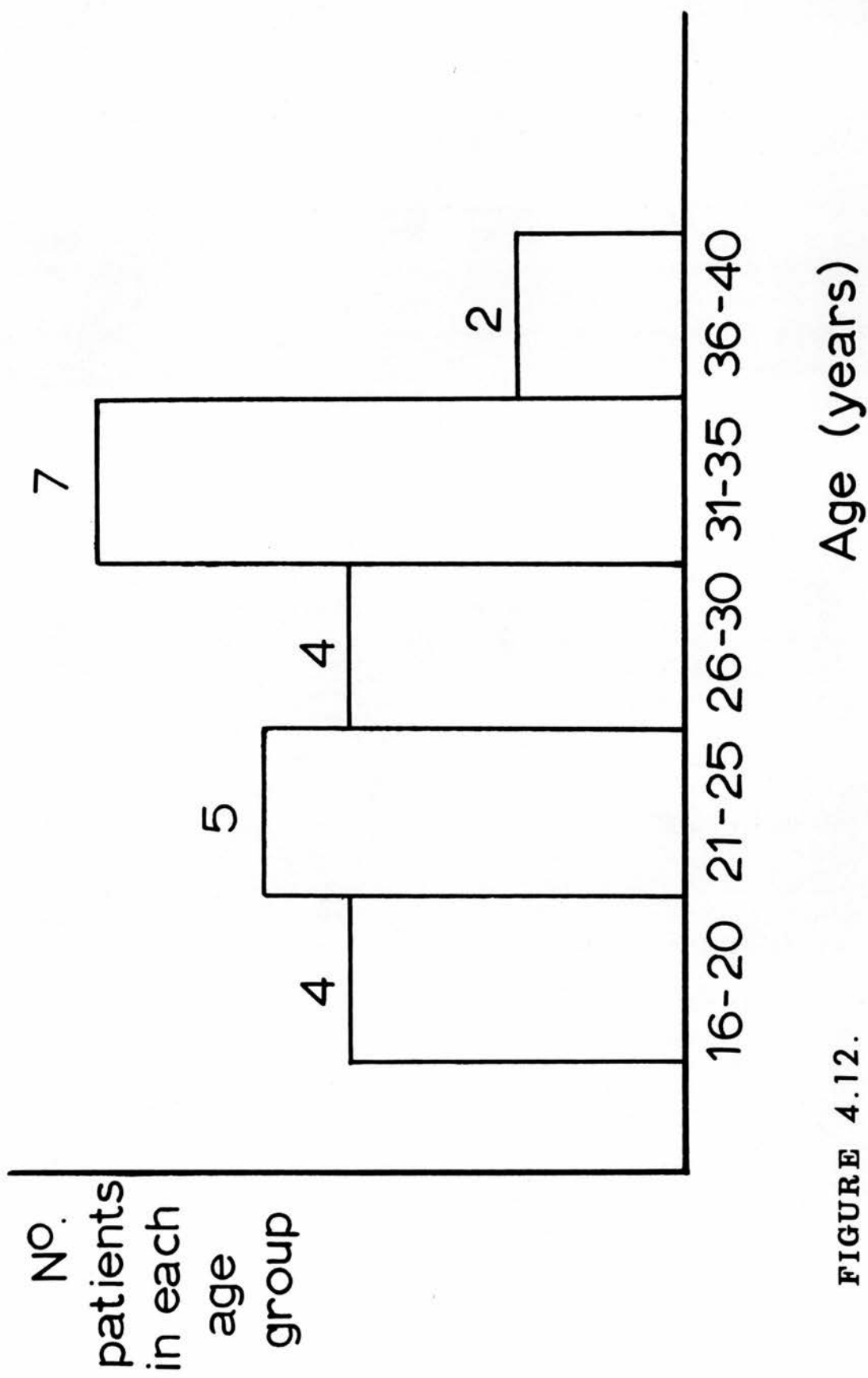


FIGURE 4.12.

of the urethritis in 13 (59.1%), but was delayed by more than four weeks in 4 (18.2%), (Figure 4.13).

In addition to the above patient with circinate balanitis but no urethritis one other patient had circinate balanitis and a further patient had an acute orchitis.

(b) Conjunctivitis and acute anterior uveitis

Fifteen patients had a conjunctivitis during the acute episode and in fourteen this occurred within one week of the onset of the arthritis. In the remaining patient the conjunctivitis preceded the arthritis by six weeks (Figure 4.14). Two patients had a mild uveitis. The one female had an acute conjunctivitis commencing a week after the onset of her urinary symptoms and one day before the onset of her arthritis, but two months later developed an acute anterior uveitis. One of the two patients not seen during his acute attack had had an acute anterior uveitis shortly after his arthritis had resolved.

(c) Arthritis

Table 4.17 shows the joints involved in these twenty-two patients. The knees and ankles were the most frequently involved joints. Low back or buttock pain and stiffness similar to that described by patients with ankylosing spondylitis was experienced by 11 (50%) patients but no patient had this as their only rheumatic symptom.

Figure 4.13 Duration of latent period from onset
of urethritis to onset of arthritis
in 20 males with Reiter's syndrome
seen personally.

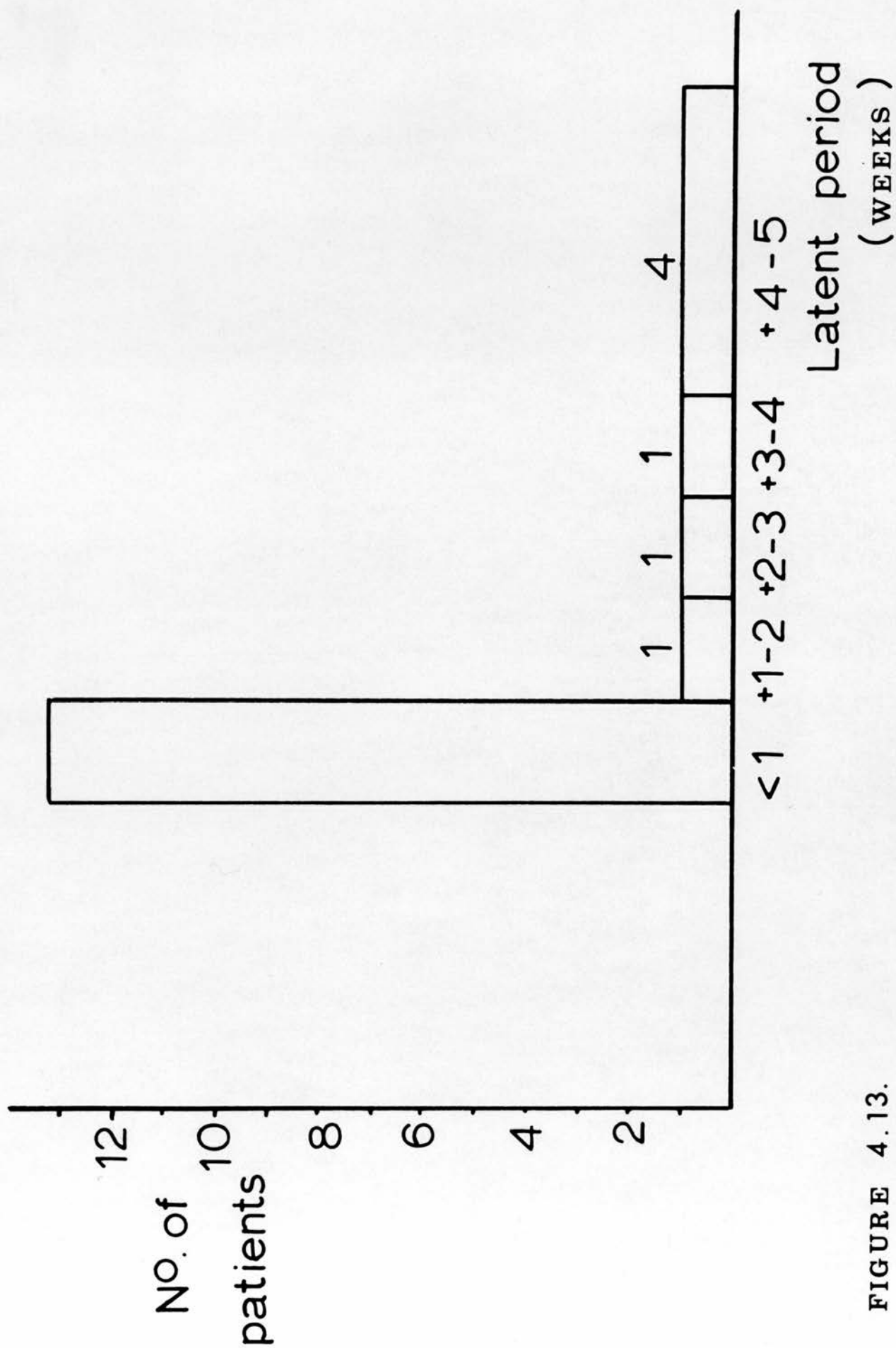


FIGURE 4.13.

Figure 4.14 Duration of latent period between onset of conjunctivitis and arthritis in 15 patients with Reiter's syndrome seen personally.

fig. 4.14

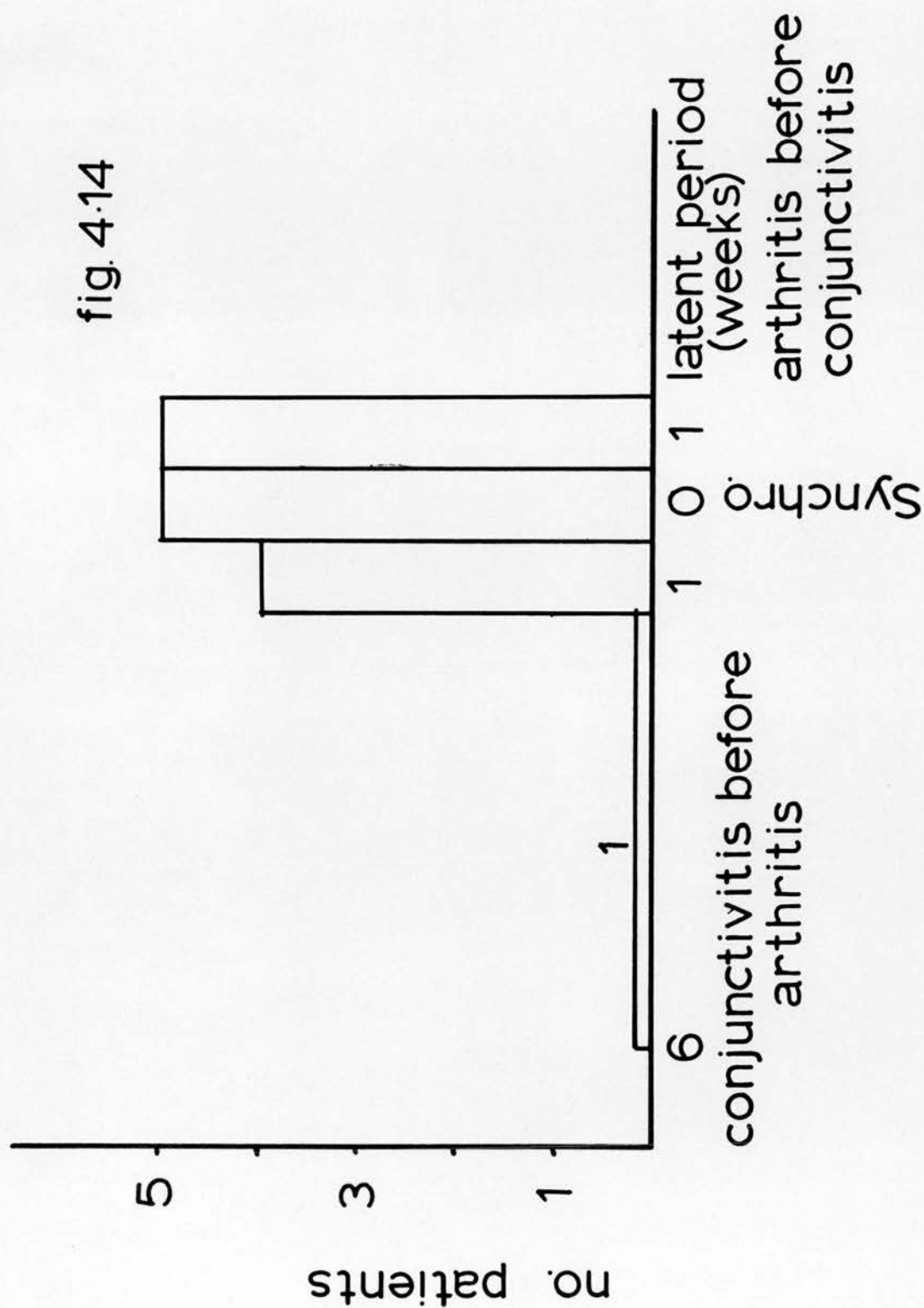


Table 4.17 Joints involved in 22 patients
with Reiter's syndrome

Joint or site affected	Number of patients with joints involved
Knee	14
Ankle	10
Buttocks	7
Heel	6
Wrist	6
Forefoot	5
Toes	5
Back	4
Shoulder	3
Achilles tendon	2
Metacarpophalangeal	2
Proximal interphalangeal	1
Hand	1
Neck	1
Temperomandibular	1

Heel pain and tenderness and "sausage toes" occurred frequently, 27.3% and 22.7% respectively. Two patients had an Achilles tendonitis. The small joints of the hands were only involved in three patients. Since most patients were only seen once and were primarily under the care of other physicians and many were permanently domiciled some distance from Liverpool, no attempt was made to determine the duration of their illness to determine the frequency of any long-term sequelae in this group.

(d) Previous Reiter's syndrome

One patient had, three years previously, a definite episode of Reiter's syndrome with a urethritis and typical arthritis occurring 10 days later (Case 4.4(iii)). Another patient (Case 4.4(iv)) two years before had had a purulent conjunctivitis in association with a Reiter's type of arthritis lasting 3 months but no symptomatic urethritis. Two years before being seen with Reiter's syndrome a third patient had an acute arthritis alone of the metacarpophalangeal joints of the left hand, lasting two weeks (Case 4.4(v)).

(e) Keratoderma blenorrhagica

Keratoderma blenorrhagica was present in three patients and in one of these three there was also involvement of the nails.

(f) Radiological sacroiliitis

All 21 male patients had anteroposterior pelvic and posteroanterior sacroiliac joint radiographs. Unilateral sacroiliitis was found in two patients (Cases 4.4(vi) and 4.4(vii)).

(g) Family history

Two patients had a family history of ankylosing spondylitis. The maternal uncle of the one female patient (Case 4.4(viii)) had been previously ascertained independently because of his ankylosing spondylitis. The second patient (Case 4.4(vii)) had a sister with previously diagnosed ankylosing spondylitis. In the previous 50 patients four were reported who had a brother with ankylosing spondylitis.

One patient seen personally had a brother who had previously had a definite Reiter's syndrome (Case 4.4(ix)). Two patients knew of relatives, one a mother and one a brother, with psoriasis.

4.4.2 Histocompatibility testing

Histocompatibility typing was performed in all 22 patients and 17 (77.3%) were found to be HLA-B27 positive. This is similar to the first 50 patients (68% were HLA-B27 positive) as were the frequencies for the other HLA antigens apart from HLA-A2 which was present in 18 (81.8%) of the 22 patients, this being significantly more frequent than in 8.2% of the 451 controls ($\chi^2_c = 10.8$; $p = 0.001$) and in the earlier

series of 50 patients with Reiter's syndrome ($\chi^2_c = 3.9$; $p = 0.049$). The frequency of HLA-A2 in the earlier series of 50 patients with Reiter's syndrome was not significantly increased when compared with the controls. The only clinical difference between the 22 patients seen personally and the earlier series of 50 patients is in the duration of follow up, in that 20 of these 22 were seen during the acute phase of their illness, whereas only eleven in the earlier series of 50 patients were seen during this phase of their illness. There is no reason to suppose that this would result in any difference in the histocompatibility antigen frequencies observed and since the diagnostic criteria for inclusion did not differ between the two parts of the series as a whole the analysis of the histocompatibility antigen frequencies has been performed in the total series of 77 patients (Table 4.18).

The frequency (71.4%) of HLA-B27 was found to be significantly more than the 8.2% in controls ($\chi^2_c = 178.36$; $p = 1.15 \times 10^{-40}$). HLA-A2 was also present in 64.9% of the total series of 77 patients compared with 43.7% of 451 controls ($\chi^2_c = 11.06$; $p = 8.8 \times 10^{-4}$). This is still significant at the 5% level even when this p value is multiplied by 24 to take account of the number of antigens tested ($p = 0.021$). No other histocompatibility antigens were present with a significantly increased frequency in the patients when allowance was made for the number of antigens tested.

Table 4.18 Histocompatibility antigen frequencies for patients with Reiter's syndrome and controls; Yates χ^2 and Woolf relative risk and χ^2 (wy^2)

HLA antigens	Patients with Reiter's Syndrome (77)		Controls (451)		Yates χ^2	p	Relative risk x	wy^2	p
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen					
A1	15	19.5	154	34.1	5.84	0.016	0.467	6.26	0.012
A2	50	64.9	197	43.7	11.06	8.8×10^{-4}	2.388	11.47	7.1×10^{-4}
A3	16	20.8	131	29.0	1.81	0.179	0.641	2.21	0.137
A9	14	18.2	88	19.5	0.01	0.920	0.917	0.07	0.791
A10	8	10.4	40	8.9	0.00	1.000	0.901	0.06	0.806
A11	13	16.9	58	12.9	0.60	0.439	1.376	0.88	0.348
A28	7	9.1	24(397)	6.0	0.50	0.480	1.554	0.96	0.327
A29	1	1.3	31(408)	7.6	3.06	0.080	0.162	3.16	0.075
AW30/31	2	2.6	23(396)	5.8	0.08	0.777	0.612	0.43	0.512
AW32	6	7.8	26(404)	6.4	0.03*	0.862	1.229	0.19	0.663
A Blank	22	28.6	130	28.8	0.00	1.000	0.998	0.00	1.000
B5	3	3.9	44	9.8	2.11	0.146	0.375	2.59	0.108
B7	10	13.0	135	30.0	8.65	0.003	0.349	8.83	0.003
B8	8	10.4	128	28.4	10.21	0.001	0.293	8.98	0.003

Table 4.18 (Cont'd)

B12	10	13.0	128	28.4	7.30	0.007	0.377	7.56	0.006
B13	0	-	23	5.1	1.44	0.230	0.118 ⁺	4.335 ⁺	1.4×10^{-5}
B14	6	7.8	33	7.3	0.02*	0.888	1.070	0.02	0.888
BW15	9	11.7	45	10.0	0.06	0.806	1.194	0.21	0.647
BW16	2(18)	11.1	3(119)	2.5	1.30	0.254	4.833	2.74	0.098
BW17	5	6.5	38	8.4	0.12	0.729	0.755	0.21	0.647
B18	6	7.8	25	5.5	0.26	0.610	1.440	0.14	0.708
BW22	2	2.6	25	5.5	0.76	0.396	0.454	1.12	0.290
B27	55	71.4	37	8.2	178.36	1.15×10^{-40}	27.973	119.24	9.5×10^{-28}
BW35	14	18.2	54	12.0	1.74	0.187	1.634	2.23	0.135
BW40	12	15.6	51	11.3	0.77	0.380	1.471	1.23	0.267
B Blank	12	15.6	133	29.5	5.71	0.017	0.441	6.13	0.013

() figures in parentheses indicate number of patients or controls tested for a given antigen.

* Yates correction not used as it would give an over correction, i.e. $(ad-bc) < \frac{1}{2}(a+b+c+d)$

+ Haldane formula used as $a = 0$

Fifteen of the 22 patients seen personally had the full triad of symptoms and signs of Reiter's syndrome, i.e. the presence of conjunctivitis in addition to the required criteria for inclusion of urethritis and arthritis. These 15 patients did not differ significantly from the remaining six patients with respect to the frequency of HLA-B27, circinate balanitis, a history of previous Reiter's syndrome, or their mean ages at the time of their Reiter's syndrome (Table 4.19). The three patients with keratoderma blenorrhagica all had the full Reiter's syndrome triad as did the patients with family histories of ankylosing spondylitis, Reiter's syndrome and psoriasis. In the total series of 77 patients there was no significant difference in the frequency of HLA-B27 between those patients with and those without conjunctivitis (Table 4.20).

There was no significant difference in the mean ages or in the incidence of conjunctivitis between the HLA-B27 positive and negative patients. All patients with other additional features were HLA-B27 positive, as were those with family histories of ankylosing spondylitis, Reiter's syndrome and psoriasis (Table 4.21). In the total series of 77 patients no significant differences were observed in the incidence of conjunctivitis, uveitis, keratoderma blenorrhagica, radiological sacroiliitis or family histories of ankylosing spondylitis and psoriasis between the HLA-B27 positive and negative patients, although all these features were more frequent in the HLA-B27 positive patients (Table 4.22).

Table 4.19 A comparison of the clinical features and frequency of HLA-B27 in 22 patients with Reiter's syndrome with and without conjunctivitis.

Clinical group	Total	Mean Age (years)	Number of patients with						
			HLA-B27	Circinate balanitis	keratoderma blenorrhagica	previous Reiter's syndrome	a family history of		
							ankylosing spondylitis	Reiter's syndrome	psoriasis
Reiter's syndrome full triad	15 (68.2%)	27.4	10 (58.9%)	1 (50.0%)	3 (100%)	1 (50.0%)	2 (100%)	1 (100%)	2 (100%)
Urethritis and arthritis alone	7 (31.8%)	30.8	7 (41.1%)	1 (50.0%)	0	1 (50.0%)	0	0	0
TOTAL	22	28.3	17	2	3	2	2	1	2

Table 4.20 Frequency of HLA-B27 in patients with and without conjunctivitis in 77 patients with Reiter's syndrome.

	Total	No. of patients HLA-B27 positive
Reiter's syndrome full triad	53	39
Urethritis and arthritis alone	24	16
TOTAL	77	55

Table 4.21 A comparison of clinical features in a total of 22 patients with Reiter's syndrome with and without HLA-B27

	Total	Mean Age (years)	Number of patients with								a family history of		
			conjunct-ivitis	uveitis	circinate balanitis	keratoderma blenorrhagica	previous Reiter's syndrome	radio-logical sacro-iliitis	a family history of				
									anky-losing spondy-litis	Reiter's syndrome	Psoriasis		
HLA-B27 positive	17 (77.3%)	28.3	10 (66.7%)	2 (100%)	2 (100%)	3 (100%)	2 (100%)	1 (50.0%)	2 (100%)	1 (100%)	2 (100%)		
HLA-B27 negative	5 (22.7%)	28.4	5 (33.3%)	0	0	0	0	1 (50.0%)	0	0	0		
TOTAL	22	28.3	15	2	2	3	2	2	2	1	2		

Table 4.22 A comparison of clinical and radiological features in a total of 77 patients with Reiter's syndrome with and without HLA-B27

	Total	Number of patients with					a family history of	
		conjunctivitis	uveitis	keratoderma blenorrhagica	radiological sacroiliitis	ankylosing spondylitis	Reiter's syndrome	
HLA-B27 positive	55 (71.4%)	39 (73.6%)	9 (90.0%)	11 (91.7%)	9 (90.0%)	5 (83.3%)	2 (100%)	
HLA-B27 negative	22 (28.6%)	14 (26.4%)	1 (10.0%)	1 (8.3%)	1 (10.0%)	1 (16.7%)	0	
TOTAL	77	53	10	12	10	6	2	

Individual Cases 4.4(i) - 4.4(ix)

Case 4.4(i) was a 34 year old insurance clerk who 3 months prior to being seen had sprained his left ankle which had become swollen. Three to four weeks later his right wrist became swollen, and subsequently he developed swelling of the small toes, and some backache with morning stiffness. At the time he was seen there was swelling of the whole of the right second toe and a tender swelling of the carpometacarpal joints of the right thumb. Six weeks prior to the onset of his arthritis he had had sexual intercourse, but denied any symptoms of urethritis. Two months after the onset his left eye became inflamed and the vision blurred. This had resolved with one week's treatment with betamethasone eye drops. His back movements were full and radiographs of his sacroiliac joints normal.

Eight years previously he had had a urethral discharge lasting a week followed a week later by a painful swelling of the right knee. Subsequently over a period of a few weeks his small toes became swollen as did his wrists and the dorsum of both hands. The fingers felt stiff but there was no swelling of these joints. Two months after the onset of this episode of arthritis he developed an acute anterior uveitis of the left eye requiring subconjunctival injections of corticosteroid and lasting about two weeks. Although this episode of arthritis resolved completely six months later the affected joints became swollen again for three to four weeks. He then remained asymptomatic until being seen personally.

His HLA typing was HLA-A2;B27.

An example of a recurrent arthritis in a man with a previous episode of Reiter's syndrome.

Case 4.4(ii) was a 35 year old computer engineer referred because of a one month history of upper lumbar backache eased by exercise and aggravated by rest. Five years previously he had had backache for two days following laying of floor tiles. Three years prior to being seen he had had a well documented episode of Reiter's syndrome with a non-specific urethritis confirmed by a venereologist followed one week later by a conjunctivitis and pain and swelling of the right wrist which took six months to completely settle. On the occasion he was seen personally there was no evidence of urethritis, conjunctivitis or peripheral arthritis apart from some slight pain on forced flexion of the right wrist. He had full spinal movements in all planes and a chest expansion of 5 cm. Radiographs of his sacroiliac joints were entirely normal.

His HLA typing was HLA-A2,B8,W35.

A man with a previous episode of Reiter's syndrome.

Case 4.4(iii) was a 39 year old seaman who was seen ten days after the commencement of a urethritis followed three days later by a swollen right knee, pain in the left forefoot and a painful left heel. A mild conjunctivitis of the left eye was also present.

Three years earlier, whilst in Lagos, he had developed a urethritis and almost a fortnight later an identical arthritis to the above with additional low back pain. This episode took three weeks to settle but two months later the arthritis recurred without symptoms of urethritis though there had been further sexual exposure. He had remained well for a further

two years when his arthritis again recurred but without symptomatic urethritis.

Spinal movements and radiographs of the sacroiliac joints were normal.

His HLA typing was HLA-A1,2;B27.

A male with recurrent Reiter's syndrome.

Case 4.4(iv) was a 29 year old male who had had one episode of urethritis four years previously. Two years before being seen personally he had had a purulent conjunctivitis of the left eye and during the next few days had developed pain and swelling of both ankles, the right knee and the proximal interphalangeal joint of the right ring finger. He was off work a total of three months and had a residual flexion deformity of the proximal interphalangeal joint of the right ring finger. There was no associated urethritis.

He was seen personally during a subsequent episode of Reiter's syndrome in which he had developed a painful, stiff, swollen right knee, a swelling on the dorsum of the right hand and tenderness under the left heel one day after a urethral discharge. He did not have a conjunctivitis. His spinal movements were normal and his chest expansion 11 cm. Radiographs of his sacroiliac joints were normal, and he was HLA-A2,9;B5,27.

A male with recurrent Reiter's syndrome.

Case 4.4(v) was a 28 year old male who two weeks after having a urethral discharge and dysuria noticed stiffness and aching of the left ankle most marked in the morning followed two weeks later by a swelling in the left midtarsal region.

This gradually improved but then the wrists became swollen, gradually settling over a further three weeks. At some time during the episode of arthritis he noticed redness of the conjunctivae.

Six years previously he had also had a urethritis alone, and three years previously a two week episode of swelling and pain of the metacarpophalangeal joints of the left hand without urethritis or conjunctivitis.

Radiographs of his sacroiliac joints were normal and he was HLA-A2,3;B7,W15.

A male with acute Reiter's syndrome who had possibly had a previous episode.

Case 4.4(vi) was a 31 year old British army staff sergeant who had noticed occasional pain in the right loin with associated stiffness for about one year. The day after developing a urethral discharge this pain became much worse and he also developed pain in the left buttock. Seven days later his right eye felt sticky and he was noted to have a mild conjunctivitis. A few days later the left wrist became swollen and tender. His back movements showed only slight restriction (forward flexion 5.5 cm, lateral flexion 3 cm) and his chest expansion was normal at 8 cm. Radiographs of his pelvis and sacroiliac joints showed a grade 2 sacroiliitis on the right, there being no abnormality in his lumbar spine radiographs.

It seems unlikely that an episode of Reiter's syndrome present for only two weeks at the time of these radiographs could account for the changes seen, but these changes may be

related to the preceding one year history of back pain and stiffness. There are, however, insufficient criteria present to make a diagnosis of definite ankylosing spondylitis.

His HLA typing was HLA-A2;B27,W40. He had a 36 year old sister with an 18 year history of ankylosing spondylitis. Her HLA typing was HLA-A2;B13,27. Full genotyping was not possible because of lack of available relatives.

An example of a male with a first attack of acute Reiter's syndrome, a history suggestive of previous mild ankylosing spondylitis and radiologically abnormal sacroiliac joints, and whose sister had definite ankylosing spondylitis.

Case 4.4(vii) was a 39 year old driver who had had a slight urethral discharge with dysuria persisting for six weeks. Three or four weeks from the onset of these urinary symptoms he developed bilateral conjunctival infection with associated grittiness, but no pain or impairment of vision, lasting two to three days. At the same time he had pain under the metatarsal heads of the right foot and in the lateral aspect of the right ankle which was also swollen. Similar symptoms developed in the left foot and the second toes of both feet became swollen. Subsequently he had pain and swelling of the metacarpophalangeal joint of the left thumb and pain without swelling in the left knee.

For the previous ten years he had had mild backache with associated morning stiffness. His back movements were normal (forward flexion 6 cm, lateral flexion 4.5 cm) and his chest expansion was 10 cm. His radiographs showed a grade 3 sacroiliitis on the right.

There was no history to suggest iritis or psoriasis and no skin lesions were present at the time he was seen.

His HLA typine was HLA-A2,9;BW16.

His 68 year old father who had previously had a heavy job repairing railway rolling stock had a 35 year history of backache and stiffness. Apart from a myocardial infarction a year earlier he was otherwise well. Radiographs of his sacroiliac joints were entirely normal. The patient's 70 year old mother was asymptomatic, had normal back movements and was not x-rayed.

An example of a HLA-B27 negative male with acute Reiter's syndrome with a previous history suggestive of ankylosing spondylitis and definite radiological abnormality of a sacroiliac joint.

Case 4.4(viii) was the only female seen in the personal series of 22 patients. She was 24 years old and recently married. On her honeymoon she had developed dysuria and frequency of micturition. One week later she developed a purulent conjunctivitis, without pain or visual disturbance, lasting two to three days. The next day she developed a painful swelling of the left knee and became pyrexial. Within a few days there was pain in the metatarsophalangeal joint of the right great toe and swelling of the right knee. Subsequently, she experienced aching in the right wrist, pain in the right temporomandibular joint, and some lumbar backache. There was no recent history of a vaginal discharge or diarrhoea. Three months before the onset of this illness she had had an impetigo of the face.

At the time she was seen three months after the onset her joints were asymptomatic, her back movements were normal and chest expansion 10 cm. She had, however, developed an acute anterior uveitis of the left eye about three weeks before and this was still symptomatic and receiving treatment.

Her HLA typing was HLA-A30/31;B18,27.

Her maternal uncle had ankylosing spondylitis and had been ascertained independently a year previously. His HLA typing was HLA-A30/31,32;B27,W40. He had a son also with ankylosing spondylitis whose HLA typing was HLA-A28,30/31;B27,W35.

An HLA-B27 positive female with Reiter's syndrome and acute anterior uveitis who had two relatives with ankylosing spondylitis and who shared the same HLA-B27 containing haplotype (P.14).

Case 4.4(ix) was a 33 year old taxi driver who had had extramarital sexual intercourse followed a month later by a urethral discharge and dysuria lasting a few days. Two months after this he developed pain in the cervical region and two weeks later the right knee and ankle became swollen and he experienced an ache in the right loin and right shoulder. At this time he was seen three months after the onset of his arthritis, the right knee was still swollen and there was tenderness under the left heel. Lumbar spinal movements were full and his chest expansion was 10 cm. Radiographs of the sacroiliac joints were normal and he was HLA-A2;BW16,27.

His 21 year old brother, who was not available at the time as he was living in Devon, had well documented hospital records of an episode of Reiter's syndrome with urethritis,

conjunctivitis and arthritis six months previously. Their deceased father had had uncomplicated psoriasis and their mother was well.

An HLA-B27 positive male with Reiter's syndrome whose brother had a similar disease.

4.5 ACUTE ANTERIOR UVEITIS

Fifty-four of the original series of 90 patients with non-granulomatous anterior uveitis (Mapstone and Woodrow, 1975) were reviewed rheumatologically. There were 33 males and 21 females. All had recent radiographs of the sacroiliac joints available. The main effect of this review was to re-categorise patients originally diagnosed as having radiological sacroiliitis alone, as having ankylosing spondylitis in view of typical but mild symptoms or in one case because of marked restriction of spinal movements in the absence of symptoms. Two female patients originally thought to have osteitis condensans ilii were found to have ankylosing spondylitis on the basis of typical symptoms and new radiographs showing definite erosion and sclerosis of the sacroiliac joints. The final diagnoses in the total group of 90 patients who constituted a consecutive series of patients attending the uveitis clinic are shown in Table 4.23.

4.5.1 Ankylosing spondylitis

(a) Ankylosing spondylitis alone

A total of 16 patients with ankylosing spondylitis alone were seen in these 90 patients. Twelve were male and four female.

(b) Ankylosing spondylitis and psoriasis

Two males were seen who had both ankylosing spondylitis and psoriasis. Neither had a nail dystrophy typical of psoriasis.

Table 4.23 Numbers of patients with and without medical conditions associated with acute anterior uveitis in 90 patients, and their prevalence with regard to sex.

Sex	Number of patients	Diseases additional to anterior uveitis														Anterior uveitis alone	
		Ankylosing spondylitis alone		Ankylosing spondylitis with psoriasis		Ankylosing spondylitis with ulcerative colitis		Reiter's syndrome*		Radiological sacroillitis alone		Psoriasis alone		Ulcerative colitis alone			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male	51	12	23.5	2	3.9	1	2.0	2	3.9	2	3.9	0	-	1	2.0	30	58.8
Female	39	4	10.3	0	-	1	2.6	0	-	0	-	2	5.1	0	-	32	82.1
TOTAL	90	16	17.8	2	2.2	2	2.2	2	2.2	2	2.2	2	2.2	1	1.1	62	68.9

* One male patient with a previous oligoarthritis alone who was HLA-B27 positive is not included in this table.

(c) Ankylosing spondylitis and chronic inflammatory bowel disease

Two patients, one male and one female had ulcerative colitis and ankylosing spondylitis. In the male patient the ulcerative colitis had preceded by two years the onset of back symptoms at the age of 30 years. Nine years after the onset of his ulcerative colitis he had had a total colectomy. He had suffered from recurrent uveitis from the age of 45 years. The female patient aged 56 years had had ulcerative colitis for 13 years, a previous episode of uveitis and denied back symptoms. She had restriction of all spinal movements with a dorsal kyphosis and a flat lumbar spine on flexion, a chest expansion of 4 cm and bilateral grade 2 sacroiliitis.

4.5.2 Reiter's syndrome

Two males were seen who had a definite history of Reiter's syndrome in the past with a typical arthritis and urethritis. One of these (Case 4.5(i)) went on without an asymptomatic interval to develop psoriasis with nail dystrophy. A third patient gave a past history at the age of 29 years of a sudden onset of a painful swelling of the right knee, followed by the left wrist and pain under the metatarsal heads. He did not have any evidence of urethritis, bowel disturbance or eye symptoms at that time. The arthritis resolved over a period of six months, leaving only deformity of the right second toe. At the time of review he was aged 44 years and had had recurrent

uveitis of the left eye for six or seven years.

4.5.3 Radiological sacroiliitis

Two males were seen who had radiological sacroiliitis without back symptoms and with normal spinal movements. One was aged 54 years with bilaterally fused sacroiliac joints, the other was aged 59 years with grade 3 sacroiliitis on the right.

4.5.4 Psoriasis

Two female patients were seen who had psoriasis without rheumatic symptoms.

4.5.5 Chronic inflammatory bowel disease

One male aged 56 years with recurrent uveitis for 15 years had ulcerative colitis starting at 21 years of age. He had no rheumatic symptoms and radiologically normal sacroiliac joints.

4.5.6 Histocompatibility typing

All 90 patients were typed for 23 HLA specificities (Table 4.24). Fifty-one of the 90 patients (56.7%) were HLA-B27 positive compared with 8.2% of the 233 controls typed at that time giving $\chi^2_c = 87.16$; $p = 1 \times 10^{-20}$. No other histocompatibility antigen was present in a significantly increased or decreased frequency in these 90 patients when compared with the 233 controls, when allowance is made for the 23 specificities tested for by multiplying the p values by 23.

The frequency of HLA-B27 in the 28 patients described above with rheumatic and other medical

Table 4.24 HLA frequencies in 90 consecutive patients with acute non-granulomatous anterior uveitis and 233 controls; Yates χ^2 and Woolf relative risk and χ^2 (wy^2)

HLA antigens	Patients with uveitis (90)		Controls (233)		Yates χ^2	p	Relative risk x	wy^2	p
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen					
A1	30	33.3	82	35.2	0.03	0.856	0.92	0.10	0.757
A2	39	43.3	109	46.8	0.62	0.432	0.87	0.31	0.521
A3	23	25.6	65	27.9	0.08	0.547	0.89	0.18	0.674
A9	18	20.0	45	19.3	0.02*	0.890	1.04	0.02	0.889
A10	10	11.1	19	8.2	0.38	0.540	1.41	0.69	0.407
A11	11	12.2	37	15.9	0.42	0.706	0.74	0.68	0.407
A28	4	4.4	12(194)	6.2	0.07	0.683	0.71	0.35	0.702
A29	6	6.7	16	6.9	0.00	1.000	0.97	0.00	1.000
AW30/31	1	1.1	12(200)	6.0	2.42	0.120	0.18	2.75	0.097
AW32	7	7.8	12	5.2	0.41	0.522	1.55	0.80	0.113
B5	6	6.7	21	9.0	0.21	0.649	0.72	0.46	0.497
B7	24	26.7	75	32.2	0.69	0.408	0.77	0.33	0.337
B8	21	23.3	74	31.8	1.83	0.176	0.65	2.20	0.139
B12	17	18.9	63	27.0	1.89	0.169	0.63	2.29	0.131

Table 4.24 (Cont'd)

B13	4	4.4	12	5.2	0.07*	0.793	0.86	0.07	0.795
B14	5	5.6	17	7.3	0.09	0.759	0.75	0.31	0.582
BW15	10	11.1	28	12.0	0.00	1.000	0.92	0.05	0.818
BW17	4	4.4	14	6.0	0.08	0.783	0.73	0.30	0.582
B18	3	3.3	10	4.3	0.01	0.943	0.77	0.15	0.697
BW22	5	5.6	13	5.6	0.00*	1.000	1.00	0.00	1.000
B27	51	55.7	19	8.2	87.16	1.02×10^{-20}	14.73	70.55	4.52×10^{-17}
BW35	6	6.7	32	13.7	2.47	0.115	0.45	2.99	0.084
BW40	5	5.6	23	9.9	1.02	0.312	0.54	1.49	0.222

() number of patients tested for each antigen

* Yates correction not used as this would result in an over correction (i.e. $\frac{1}{2}(a + b + c + d) > (ad - bc)$)

conditions is shown in Table 4.25. Many of the figures are small, but the frequency of HLA-B27 in the 16 patients with ankylosing spondylitis alone is similar to that found in 119 patients with ankylosing spondylitis ascertained independently. Three of the four patients with psoriasis or ulcerative colitis in association with ankylosing spondylitis were HLA-B27 positive. Both patients with Reiter's syndrome and the one patient with a peripheral arthritis typical of that condition but no associated extra articular disease were all HLA-B27 positive. One of the two males with radiological sacroiliitis alone was HLA-B27 positive.

Both female patients with psoriasis alone were HLA-B27 positive. The one male patient with ulcerative colitis alone was HLA-B27 negative.

Of the remaining 62 patients 28 (45.2%) were HLA-B27 positive, which compared with 8.2% of 233 controls gives $\chi^2_c = 47.34$; $p = 6 \times 10^{-12}$, 13 of these 28 patients were male and 15 female. The frequency of HLA-B27 in males and females is of similar order in the total series and in the 62 patients with clinical disease other than uveitis.

Table 4.25

The frequency of HLA-B27 in 90 patients with acute anterior uveitis with respect to the presence or absence of associated medical conditions

HLA-B27	Sex	Number of patients	Percent of patients	Diseases additional to anterior uveitis														Anterior uveitis alone	
				Ankylosing spondylitis alone		Ankylosing spondylitis with psoriasis		Ankylosing spondylitis with ulcerative colitis		Reiter's syndrome*		Radio-logical sacro-iliitis		Psoriasis alone		Ulcerative colitis alone			
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Positive	Male	30	56.7	11	87.5	2	100.0	0	50.0	2	100.0	1	50.0	0	100.0	0	-	13	45.2
	Female	21		3		0		1		0		0		2		0		15	
Negative	Male	21	43.3	1	12.5	0	-	1	50.0	0	-	1	50.0	0	50.0	1	100.0	17	54.8
	Female	18		1		0		0		0		0		0		0		17	
TOTAL		90	100.0	16		2		2		2		2		2		1		62	

* One male patient with a previous oligoarthritis alone is not included in this table

Individual Case 4.5(i)

A 30 year old male who had had one episode of acute anterior uveitis. Fourteen years before he had had soreness and redness of the eyes without disturbance of the vision. At the same time he had dysuria but no urethral discharge. One week later an ankle and shoulder became very painful and after a further four weeks the left knee became swollen, painful and stiff. At the same time he experienced pain and stiffness in the lower dorsal spine. He noted a small patch of yellow discolouration of one finger and one toe nail. Later he developed marked onycholysis and hyperkeratosis of all the nails which has persisted since that time. He developed a rash on the palms and soles of the feet, the left arm and the chest, which has also persisted ever since. His arthritis settled over several months and he remained asymptomatic from his joints until about a year after his episode of uveitis when he noted right heel pain and morning stiffness in the left buttock.

When seen one year after his acute anterior uveitis he had an erect posture, normal spinal movements and a chest expansion of 3.5 cm. He also had psoriasis of the skin with gross hyperkeratosis of the finger and toe nails. Radiographs of the sacroiliac joints revealed no definite abnormality, other than that the left sacroiliac joint appears widened compared with the radiographs taken a year before.

His HLA typing was HLA-A1;B27

4.6 FAMILY STUDIES

In a total of 36 families with an affected proband genotyping was possible in the proband and at least one other relative with a related disease.

4.6.1 Families with more than one person with ankylosing spondylitis alone

In 13 of these families more than one person had ankylosing spondylitis alone (Table 4.26). In six of these 13 families two or more siblings were affected. In all six families two or more affected siblings in each family had inherited the same HLA-B27 haplotype. In two of these six families three siblings were affected giving 10 sibling pairs, each pair having the same HLA-B27 haplotype. In eight of these 10 sibling pairs it is possible to determine if the other histocompatibility haplotype is also shared by the affected individuals. Two sibling pairs have to be excluded as one of the affected siblings is HLA-B27 homozygous (Pedigree P.6). Of the remaining eight sibling pairs six pairs (75%) share the same total genotype whilst two do not. This frequency of sharing the total genotype is not significantly different from the 50% expected.

In eight families a parent and one child both had ankylosing spondylitis alone. In all eight instances the affected individuals had inherited the same HLA-B27 haplotype.

One family is of special interest (Pedigree P.6). In this family the proband (IV₁) had ankylosing

Table 4.26 Genotypes of affected persons in families with more than one person with ankylosing spondylitis alone

Pedigree Number	Generation				
	I	II	III	IV	V
P.1	2,27/? ,W15+	2,27/3,7*+			
P.2		(W32,27/1,8 (W32,27/10,W15 (W32,27/10,W15*			
P.3	-,27/9,12	-,27/3,W22*			
P.4		(W28,27/10.8* (W28,27/10.8			
P.5		(W28,27/10,W18* (W28,27/10,W18			
P.6				(2,27/2,27* (2,27/11,5 (2,27/11,5	
P.7	2,27/3,7	2,27/1,8*			
P.8		(2,27/1,8 (2,27/1,8	2,27/3,7*		
P.9	9,27/1,7	9,27/3,W5*			

Table 4.26 (Cont'd)

P.10		2,27/3,7	2,27/2,15* 2,27/9,17		
P.11				W30/31,27/ W32,W10*	W30/31,27/ W28,W5
P.12	2,27/W32,14	2,27/2,W40*+			
P.13		(3,27/10,W22* (3,27/10,W22			

* proband of family study

+ female

{ siblings

spondylitis alone and his two brothers (IV₄ and IV₅) had been previously diagnosed elsewhere as having the same condition. None of them had any other related disorder. Their parents (III₁ and III₂) who were second cousins, were unaffected both clinically and radiologically. The parents were both HLA-B27 positive having one common haplotype of HLA-A2;B27. The other haplotype was different. The proband was HLA-A2;B27 homozygous, his two brothers were both HLA-A2;B27/A5,B11. They had inherited the HLA-A2,B27 haplotype from their father and the HLA-A5,B11 haplotype from their mother.

4.6.2 Families with one patient with ankylosing spondylitis and a relative with a related condition

(a) Reiter's syndrome

One family (Pedigree P.14), was seen in which a girl with Reiter's syndrome (V₂) and her uncle (IV₂) with ankylosing spondylitis were ascertained independently. In addition the proband's cousin (V₁) had ankylosing spondylitis. Genotyping shows all three to have the same HLA-B27 haplotype. The parents of the proband with Reiter's syndrome were third cousins.

(b) Psoriatic arthritis

One family (Pedigree P.15) was seen in which a proband (II₂) with psoriasis and ankylosing spondylitis had a father (I₁) with ankylosing spondylitis alone. Both had inherited the same HLA-B27 haplotype. The proband's mother had psoriasis but was not available for personal study.

A further family (Pedigree P.16) was seen in which a proband (II_1) with ankylosing spondylitis also had a small joint peripheral arthritis (Case 4.1(iv) Section 4.1). His father (I_1) had peripheral psoriatic arthritis. Neither was HLA-B27 positive. The proband and his father had the haplotype A1B7 in common.

A third family (Pedigree P.17) was seen in which the proband (II_6) had both ankylosing spondylitis and episodes of acute anterior uveitis. His sister (II_3) had peripheral psoriatic arthritis. Their HLA genotypes were identical.

(c) Psoriasis

Four families were seen in which a person with ankylosing spondylitis had a relative with psoriasis. In addition two families were seen in which a person had ankylosing spondylitis and acute anterior uveitis had a relative with psoriasis. In two instances (e.g. Pedigree P.17) the two affected siblings had both inherited the same HLA-B27 haplotype. In three families (Pedigrees P.19, P.20 and P.21) the individuals with psoriasis were not HLA-B27 positive whereas the individual with ankylosing spondylitis was HLA-B27 positive. In the remaining family (Pedigree P.22) the person with psoriasis (II_2) was HLA-B27 positive but this had been inherited from her mother (I_2) who had radiological sacroiliitis alone and not from her father (I_1) who had clinical and radiological ankylosing spondylitis.

(d) Ankylosing spondylitis with inflammatory bowel disease

Five families were seen in which an individual with ankylosing spondylitis had a relative with both ankylosing spondylitis and chronic inflammatory bowel disease. A further family was seen in whom an individual with ankylosing spondylitis and acute anterior uveitis had a relative with ankylosing spondylitis and Crohn's disease. In four of these families (Pedigrees P.22, P.23, P.21 and P.24) the affected individuals in each family had inherited the same HLA-B27 haplotype. In one (Pedigree P.25) the proband (II₁) with ulcerative colitis and ankylosing spondylitis was not HLA-B27 positive whereas his brother (II₂) with ankylosing spondylitis alone was HLA-B27 positive. They both had the haplotype A2B12 in common.

In the sixth family (Pedigree P.26) neither sibling with ankylosing spondylitis (IV₁ and IV₂) was HLA-B27 positive. They had the haplotype A2B7 in common but the other HLA haplotype was different. Their parents were second cousins.

(e) Inflammatory bowel disease alone

Two families were seen in which an individual with ankylosing spondylitis alone had a relative with chronic inflammatory bowel disease alone. In one of them (Pedigree P.23) the person with ankylosing spondylitis (I₁) had been HLA-B27 positive but his son with Crohn's disease (II₅) had not inherited this

haplotype. In the second family (Pedigree P.26) the proband (IV₂) with ankylosing spondylitis alone was not HLA-B27 positive. He had inherited the haplotype A2B7 from his mother with ulcerative colitis.

(f) Acute anterior uveitis

Two families were seen in which an individual with ankylosing spondylitis alone had a relative with acute anterior uveitis. In one (Pedigree P.27) the son (II₁) with ankylosing spondylitis had inherited the haplotype A1,B27 from his mother who had acute anterior uveitis (I₂). In the second family (Pedigree P.25) a male with ankylosing spondylitis (II₂) was HLA-B27 positive and his sister (II₃) with a history of acute anterior uveitis was HLA-B27 negative. They did not have the other HLA haplotype in common.

(g) Peripheral oligoarthritis

Three families were seen in which an individual with ankylosing spondylitis alone had a relative with an inflammatory arthritis of one or both knees. In two of these (Pedigrees P.28 and P.29) the son with oligoarthritis had inherited the same HLA-B27 haplotype as his father with ankylosing spondylitis. In the third family (Pedigree P.30) no common haplotype had been inherited by the affected siblings (II₁ and II₂). The individual with oligoarthritis (II₁) had inherited the haplotype A1,B8 from his deceased father (I₁) who had had ankylosing spondylitis.

4.6.3 Families with a person with Reiter's syndrome and a relative with a related condition

(a) Psoriasis

One family (Pedigree P.31) was seen in which a proband with Reiter's syndrome (II_3) had a brother with psoriasis (II_2). They had not inherited a common haplotype.

(b) Ankylosing spondylitis

(See 4.6.2(a))

4.6.4 Families with a person with psoriatic arthritis and a related condition

(a) Psoriatic arthritis

One family (Pedigree P.32) was seen in which the proband (III_4) with peripheral psoriatic arthritis had a paternal uncle (II_3) with a similar arthritis. They were both HLA-B27 positive but genotyping shows that they had not inherited the same HLA-B27 haplotype, but had inherited different HLA-B27 haplotypes from a common ancestor (I_1).

(b) Ulcerative colitis

One family (Pedigree P.33) was seen in which the proband (II_1) with psoriasis and ankylosing spondylitis had a paternal aunt (I_1) with ulcerative colitis. The HLA-B27 haplotype had been inherited from her mother (I_2).

(c) Ankylosing spondylitis

(See 4.6.2(b))

KEY TO PEDIGREES

Key to Pedigrees:-



MALE



FEMALE



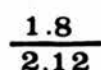
PROBAND



FOUR SIBLINGS



DEDUCED HAPLOTYPE



HLA TYPE, THE HORIZONTAL LINE SEPARATING THE HAPLOTYPES, "w" PREFIXES OF "WORKSHOP" SPECIFICITIES EXCLUDED FOR CLARITY



DECEASED



ANKYLOSING SPONDYLITIS



RADIOLOGICAL SACROILIITIS



OLIGOARTHRITIS OR ENTHESOPATHY



ULCERATIVE COLITIS



CROHN'S DISEASE



PSORIASIS



PSORIATIC ARTHRITIS

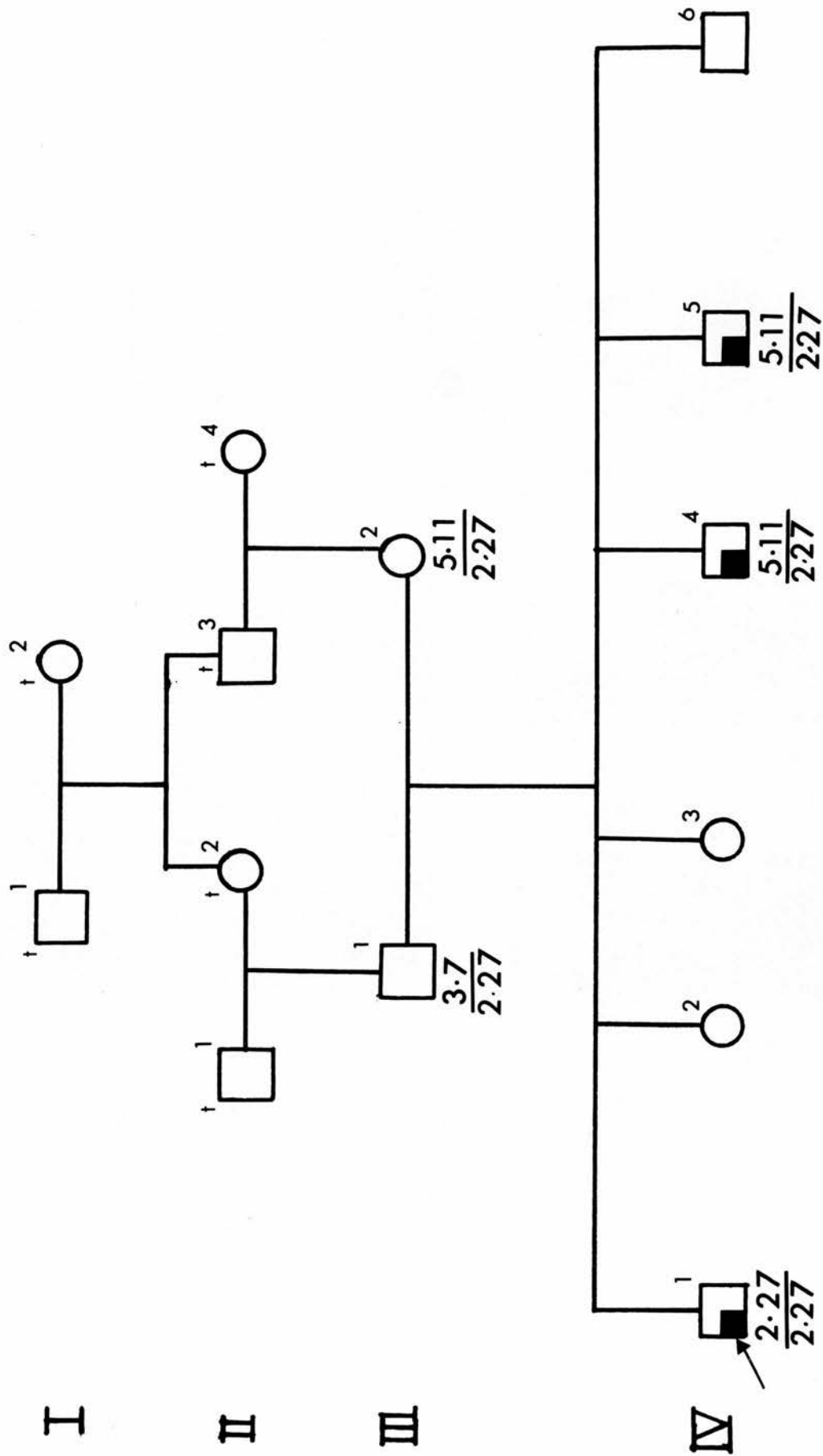


REITER'S SYNDROME

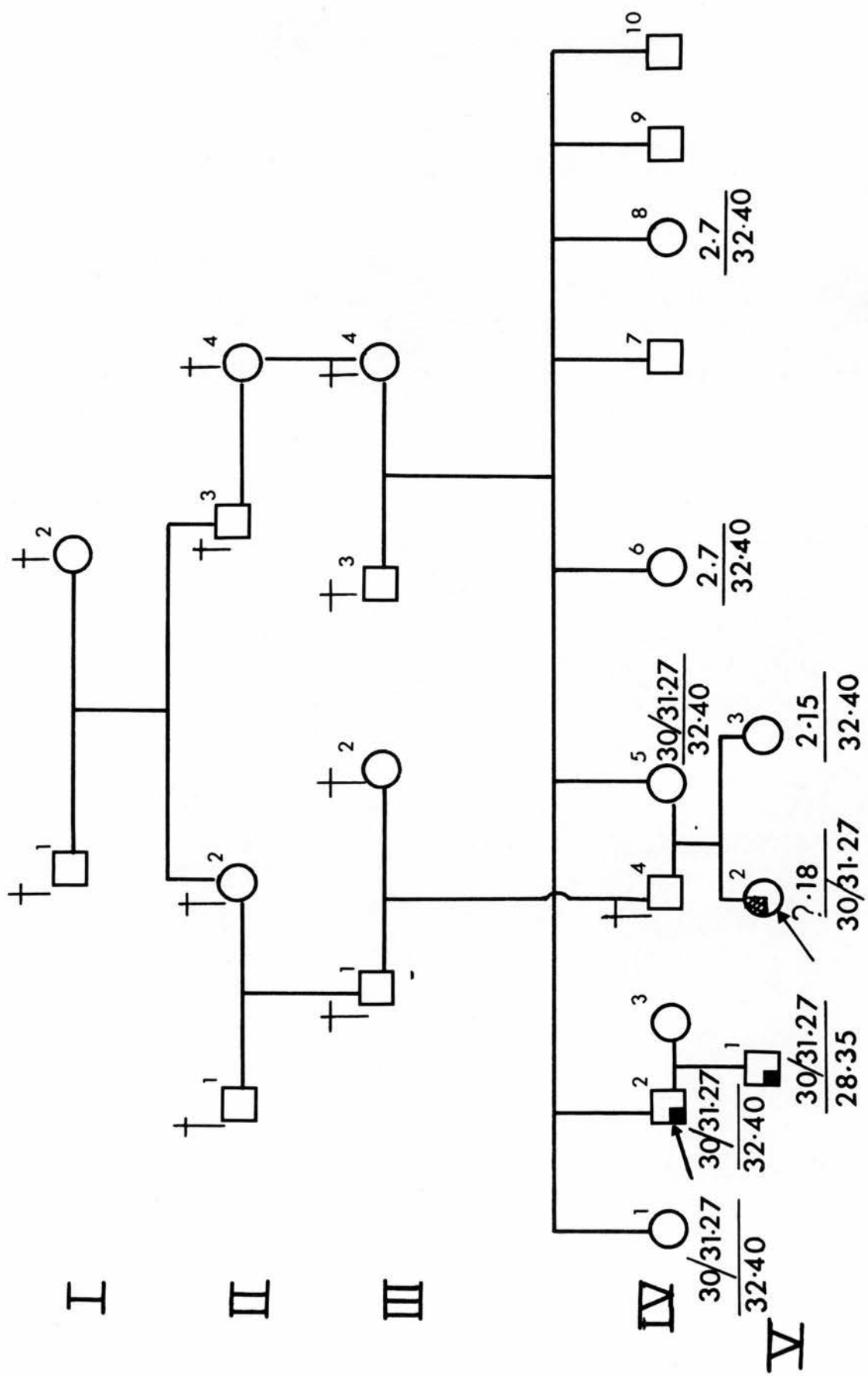


ACUTE ANTERIOR UVEITIS

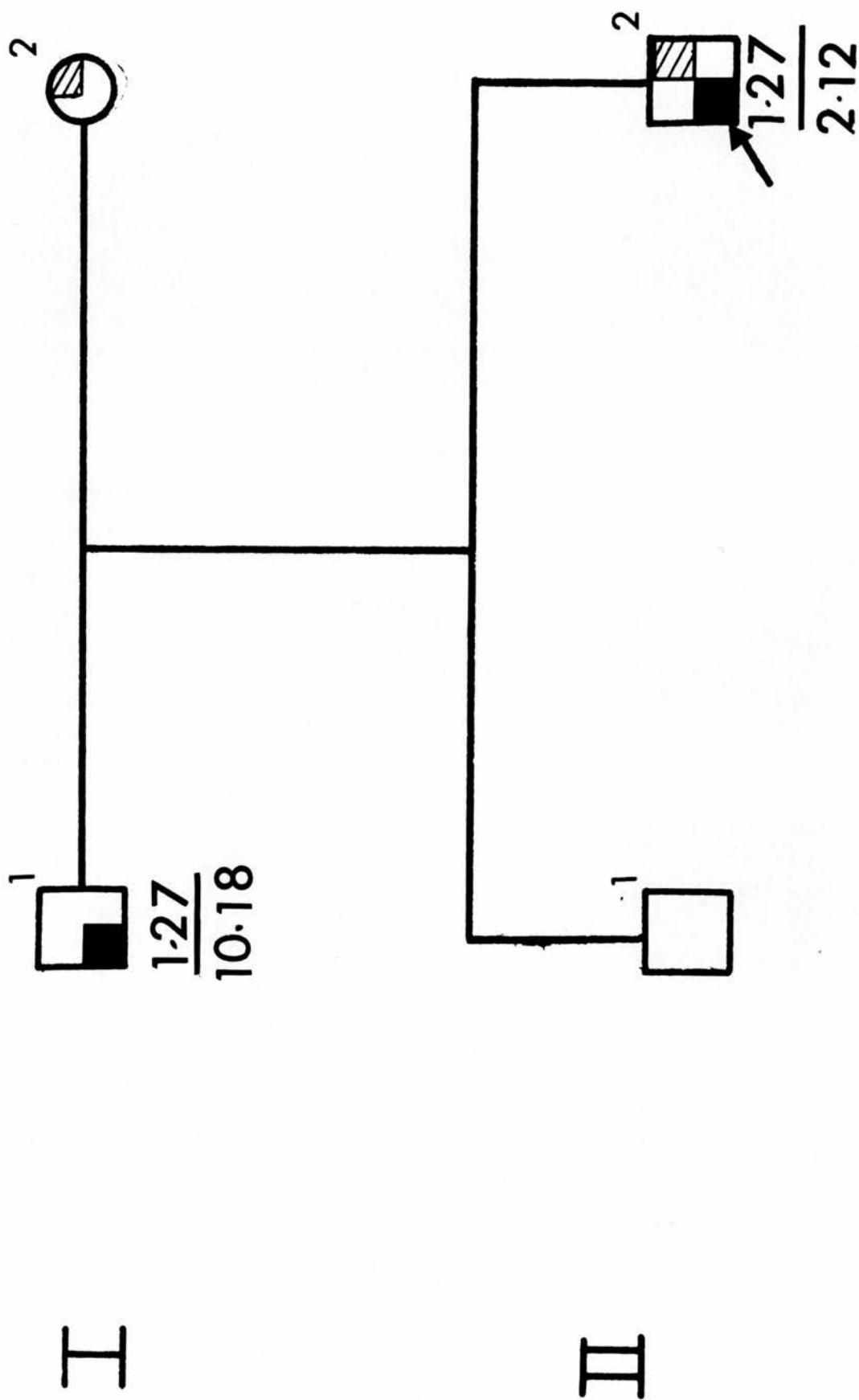
PEDIGREE P.6



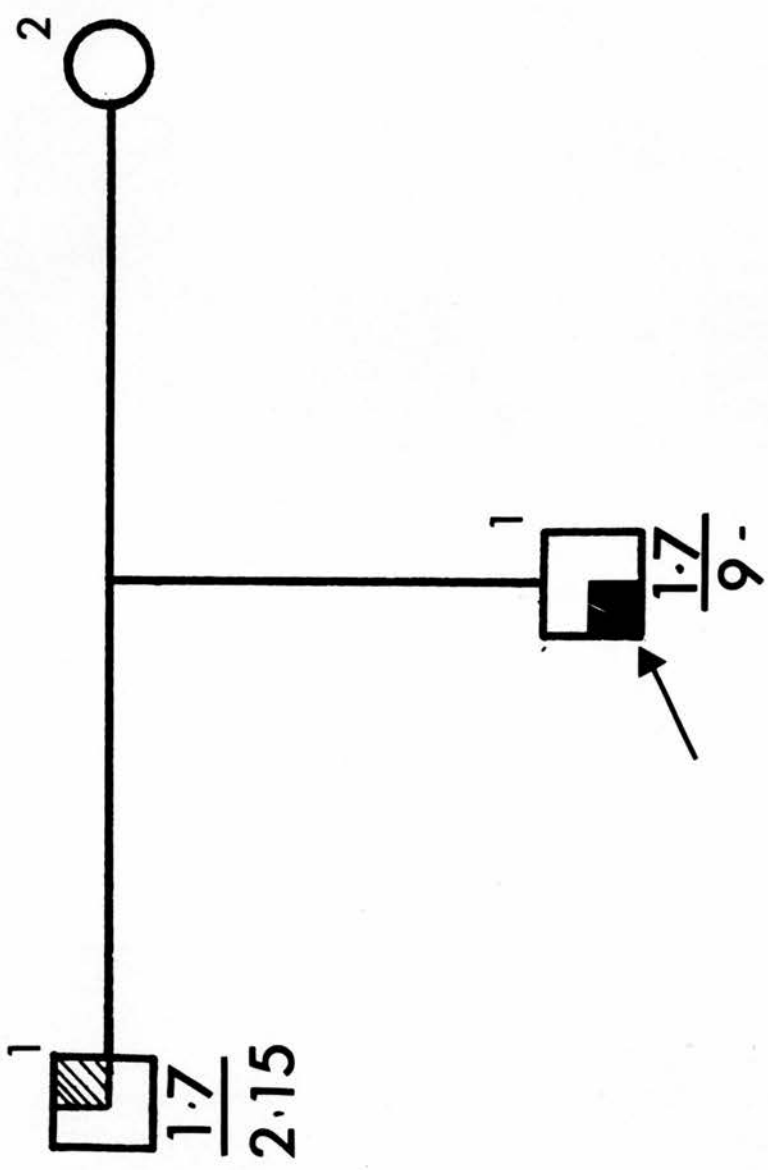
PEDIGREE P.14



PEDIGREE P.15



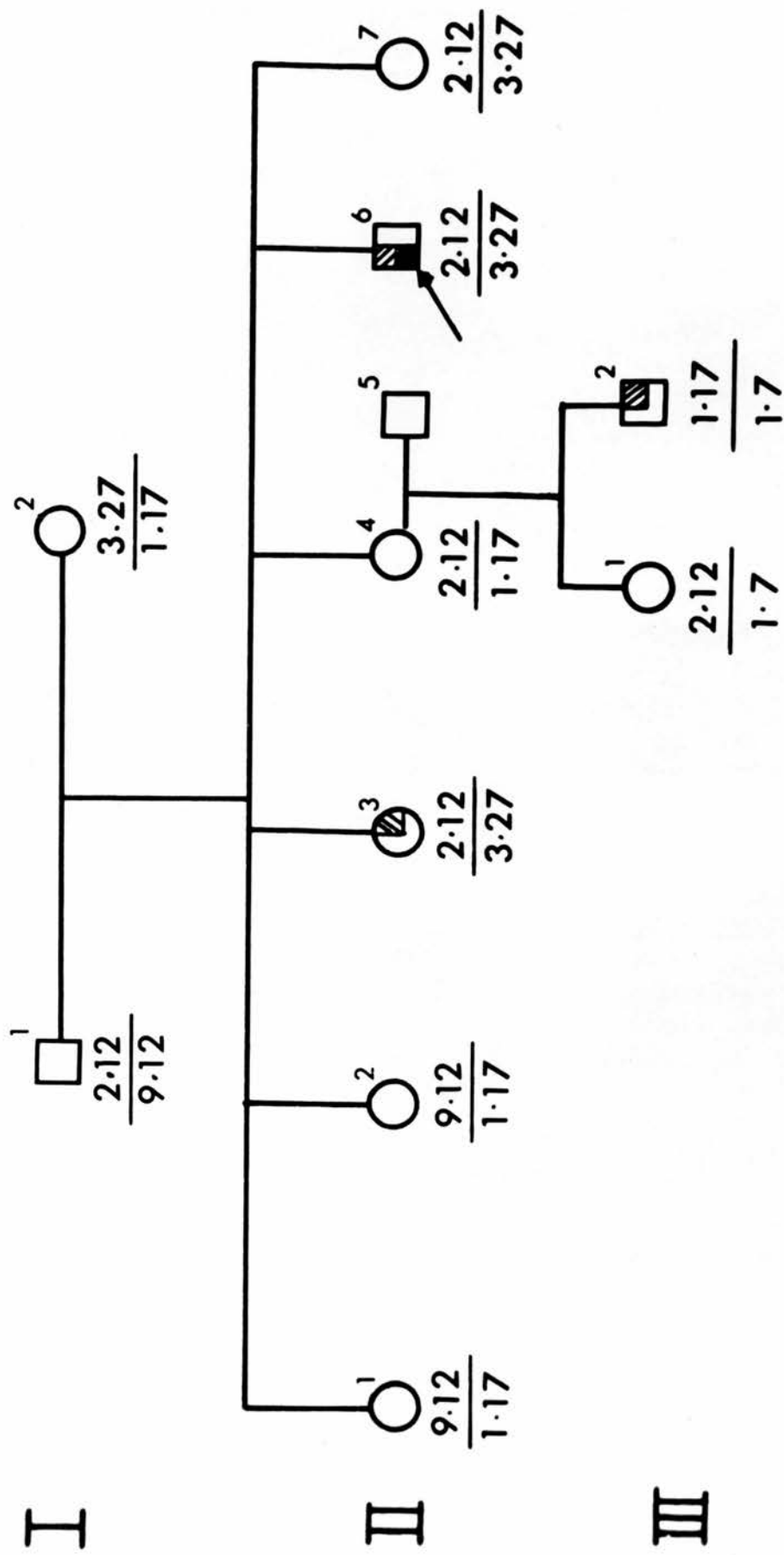
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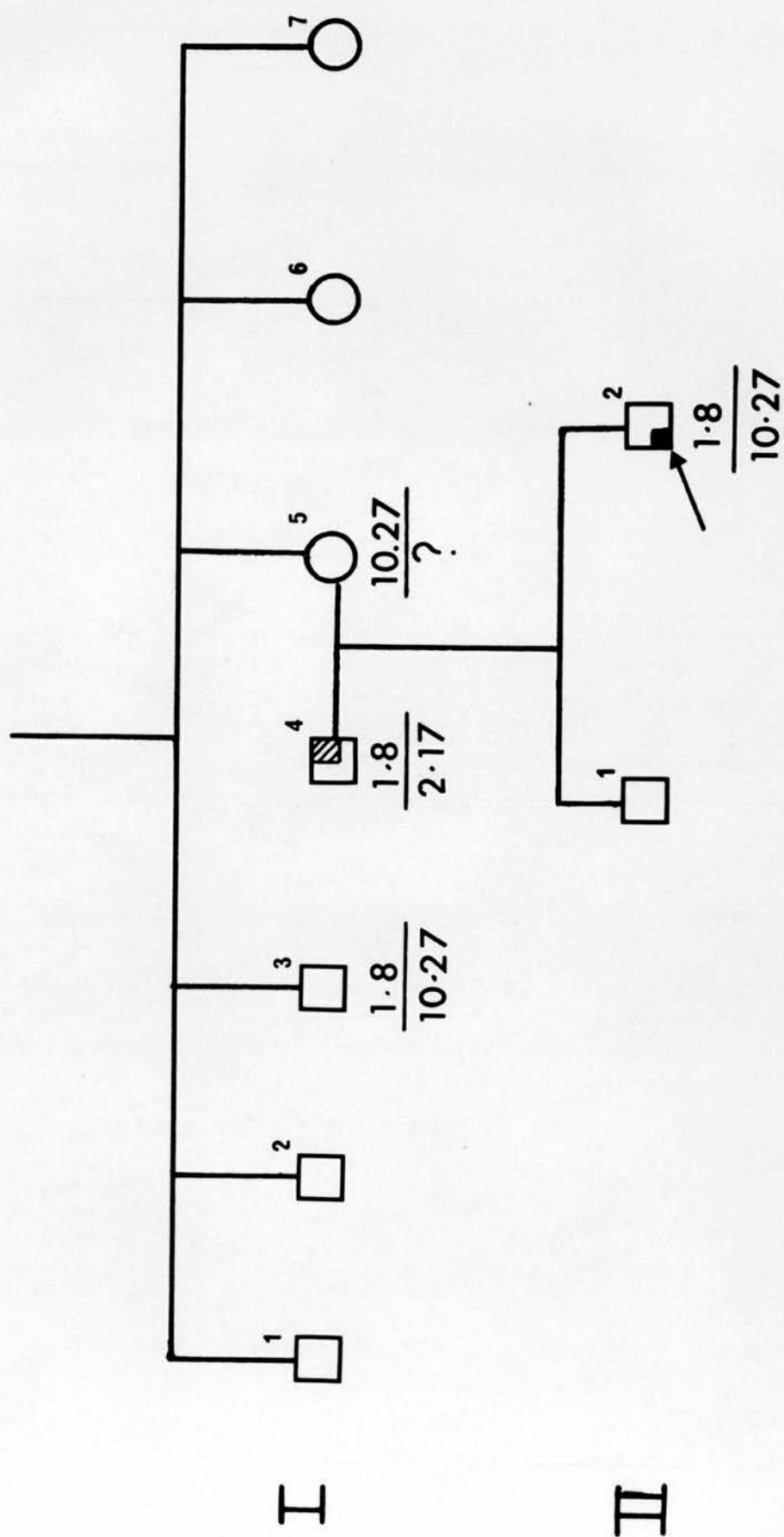
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II

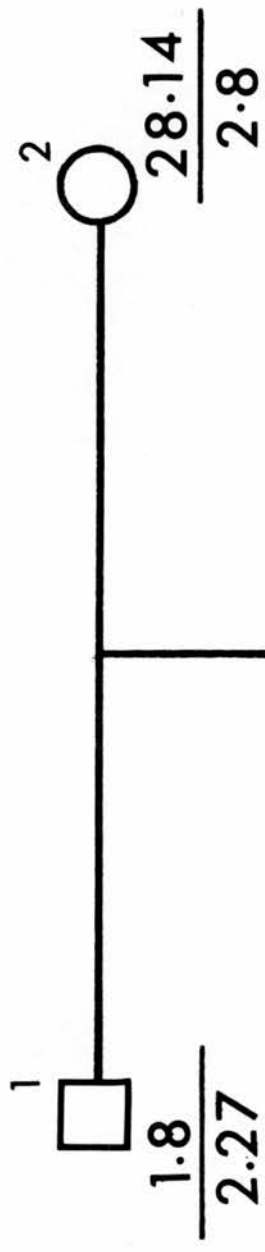
PEDIGREE P.17



PEDIGREE P.19



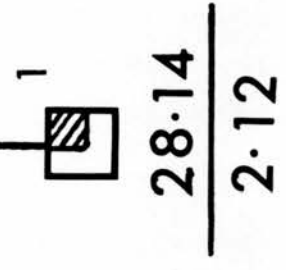
PEDIGREE P.20



I

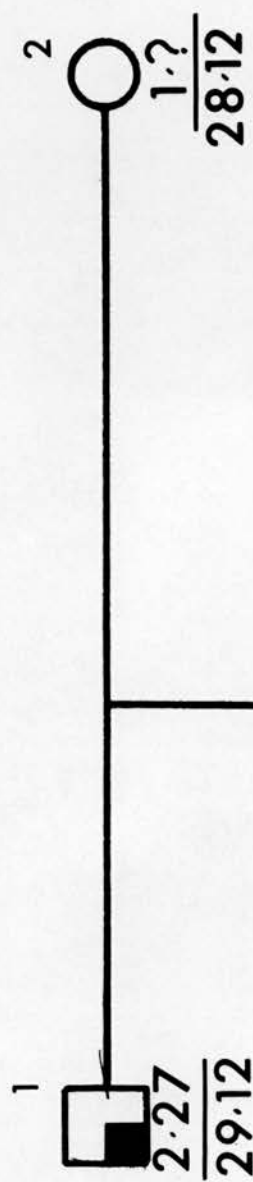


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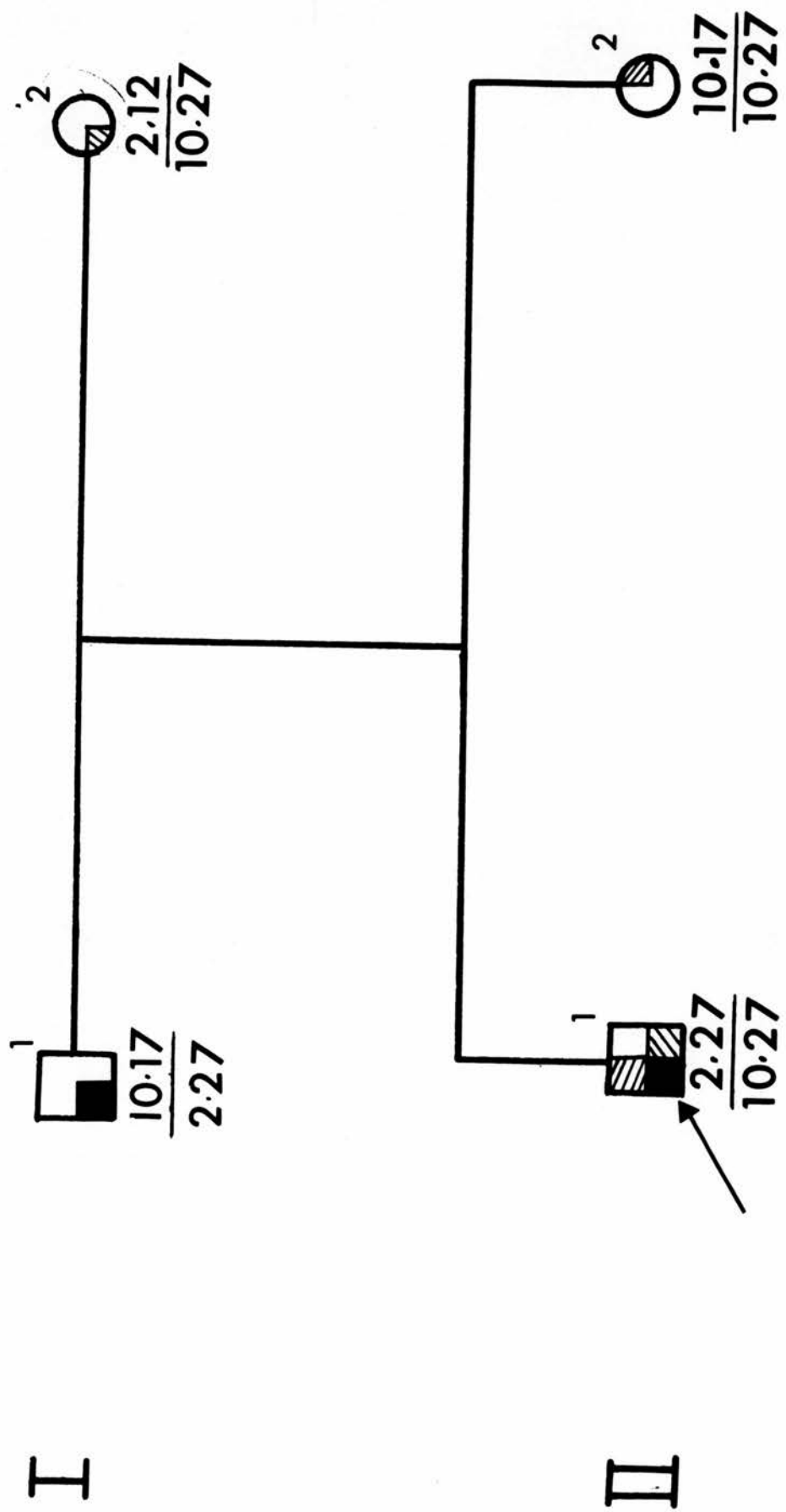


III

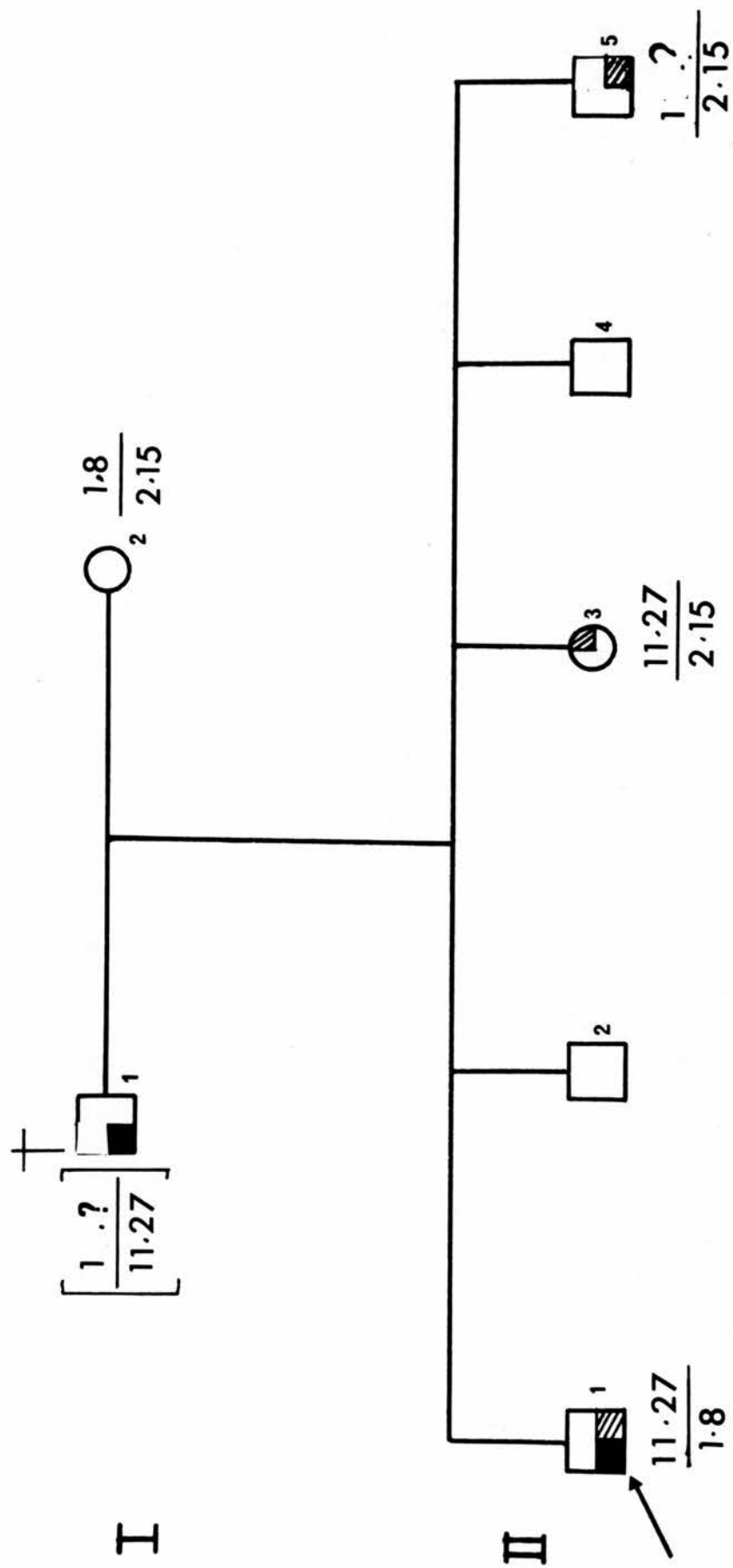
PEDIGREE P.21



PEDIGREE P.22



PEDIGREE P.23

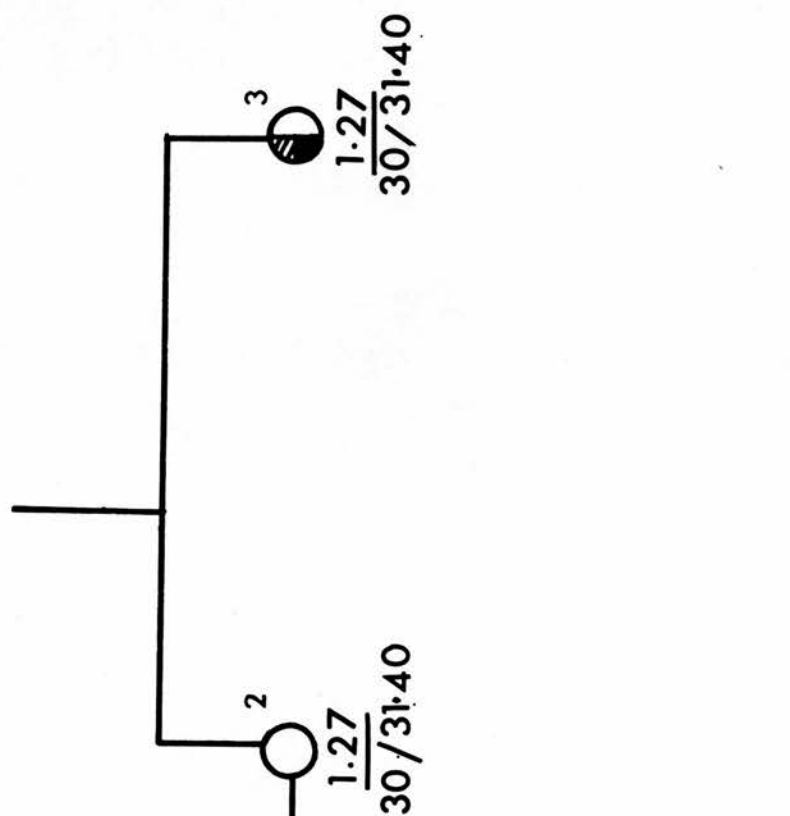
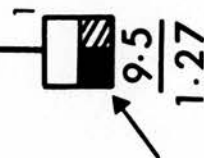


PEDIGREE P.24

I



II

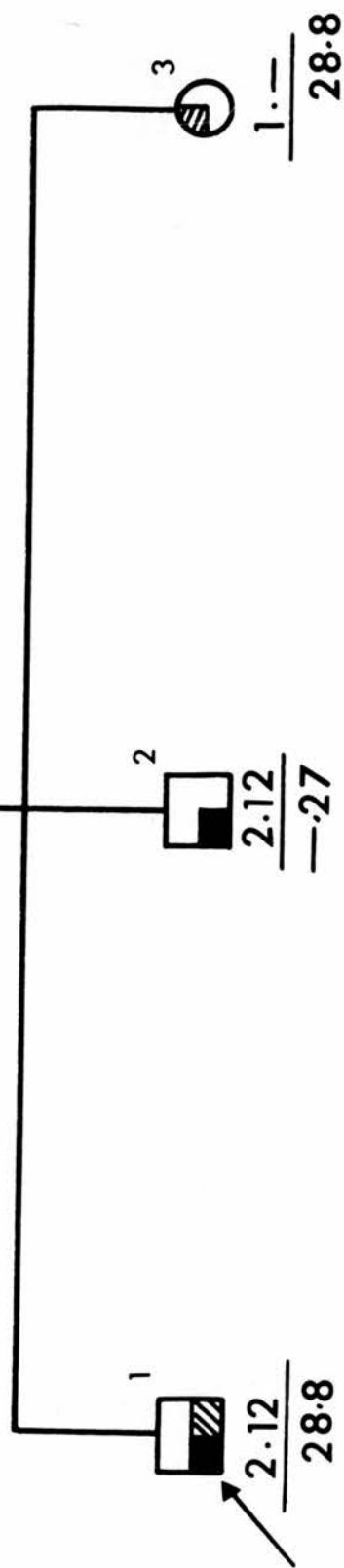


PEDIGREE P.25

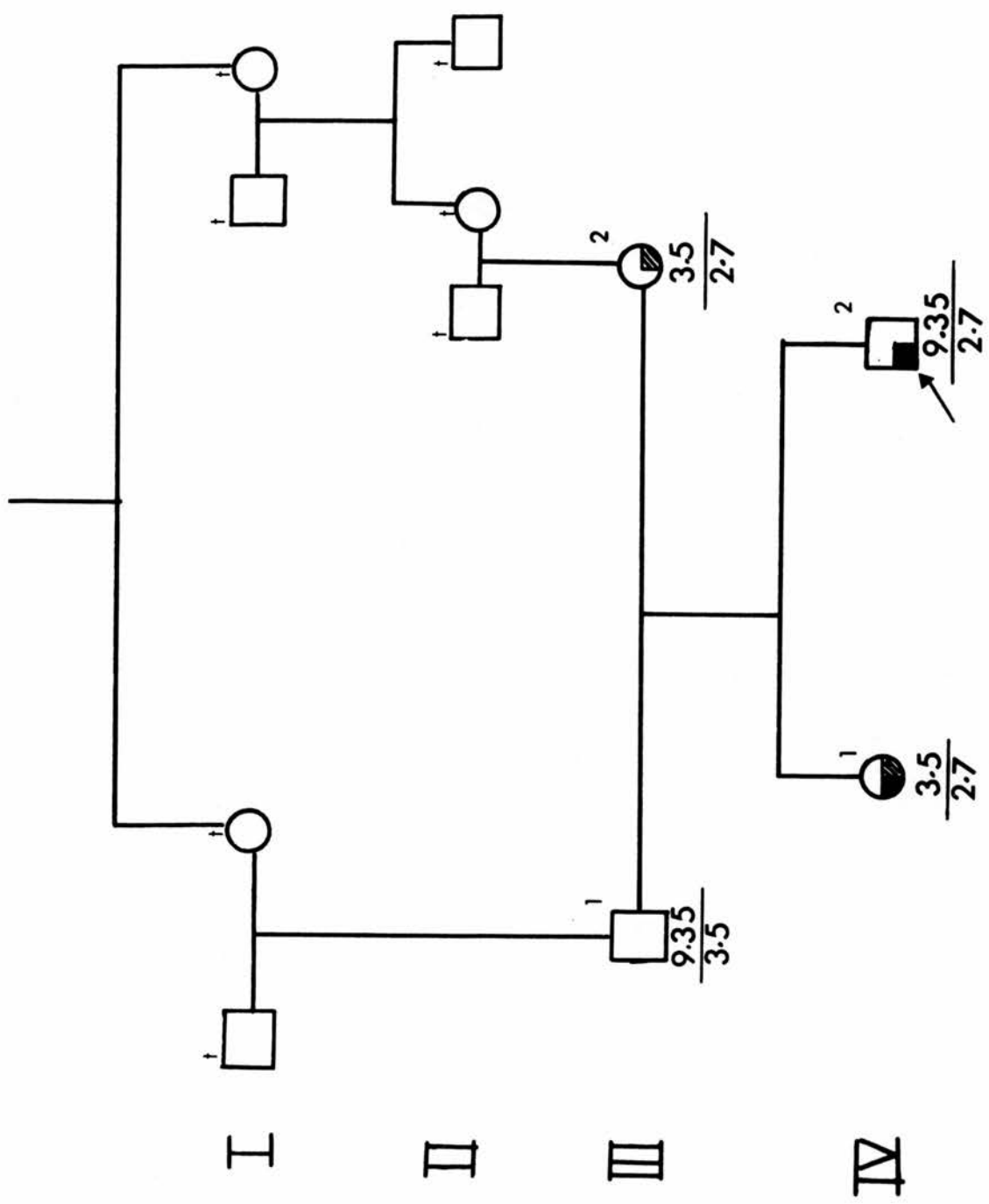
I

$$\left[\frac{2.12}{1.-} \right] \quad \left[\frac{28.8}{-27} \right]$$

II

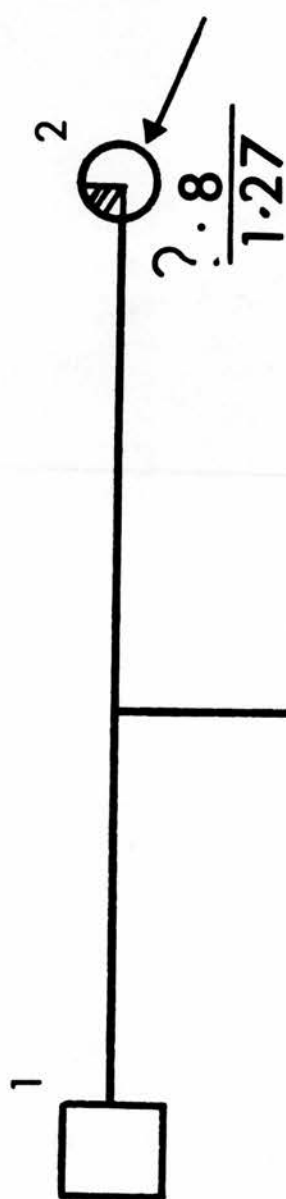


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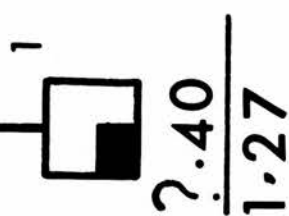


PEDIGREE P.27

I



II



PEDIGREE P.28

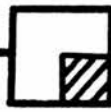
2

¹


$$\frac{1.8}{32.27}$$

I

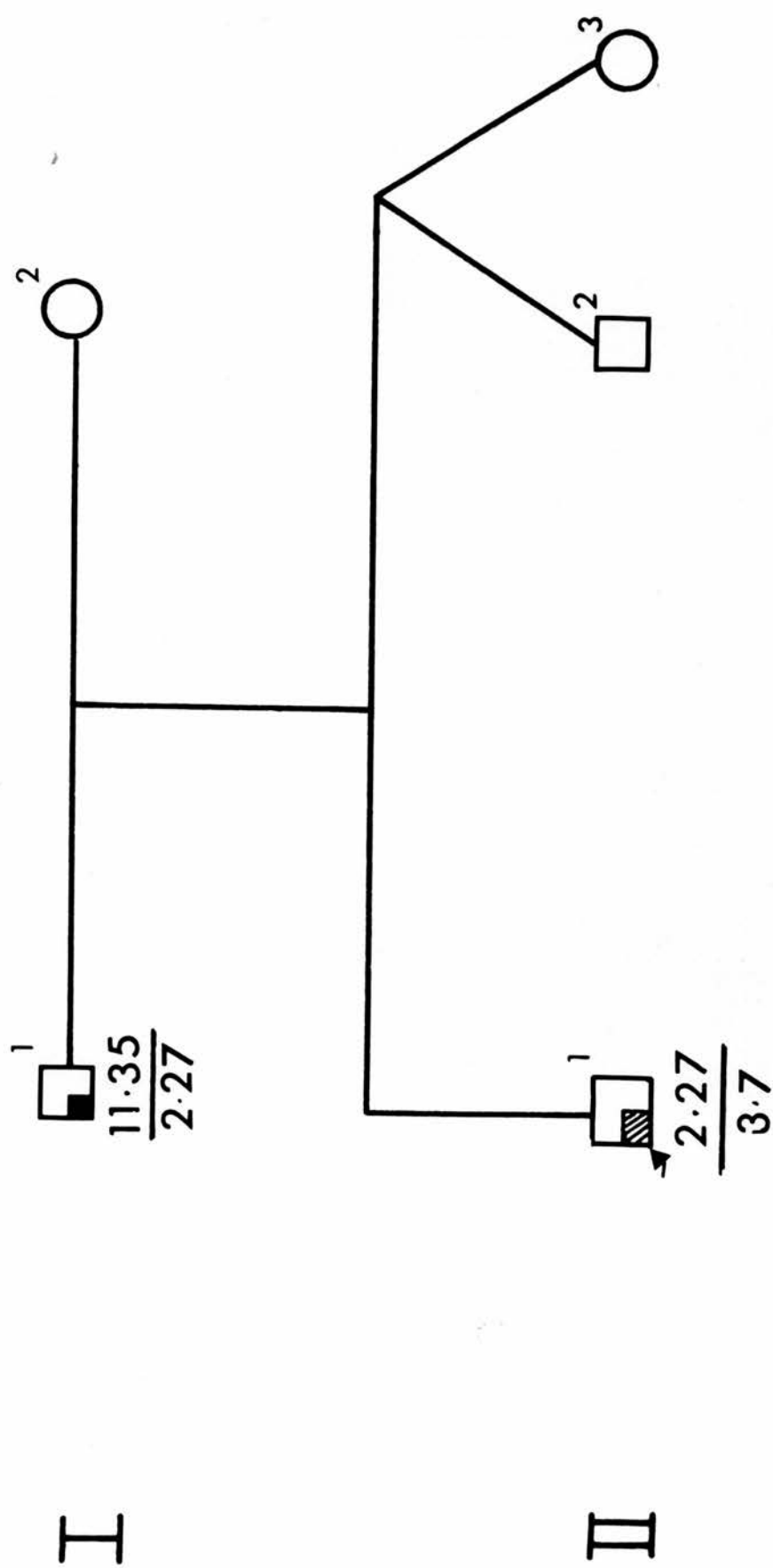
¹


$$\frac{32.27}{30/31.7}$$

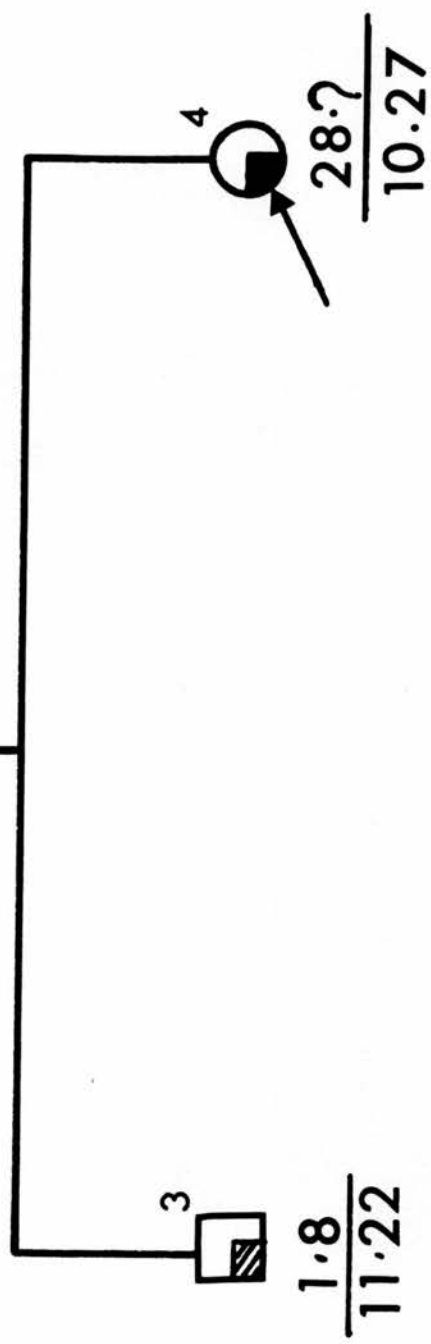
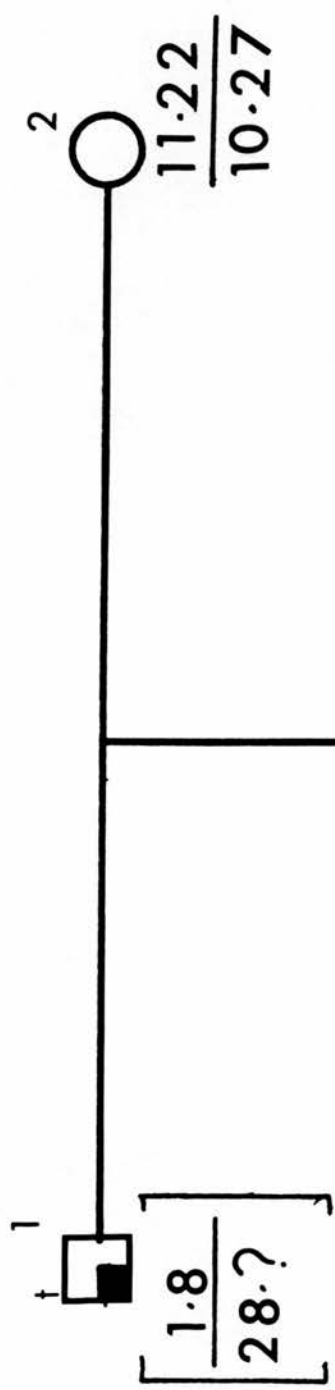
↗

II

PEDIGREE P.29

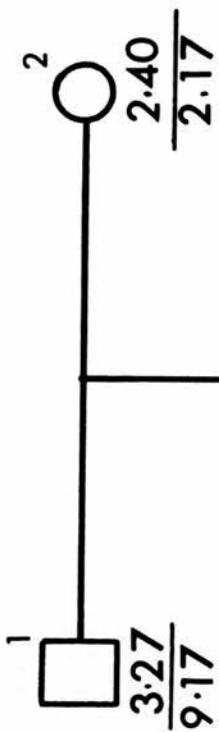


PEDIGREE P.30

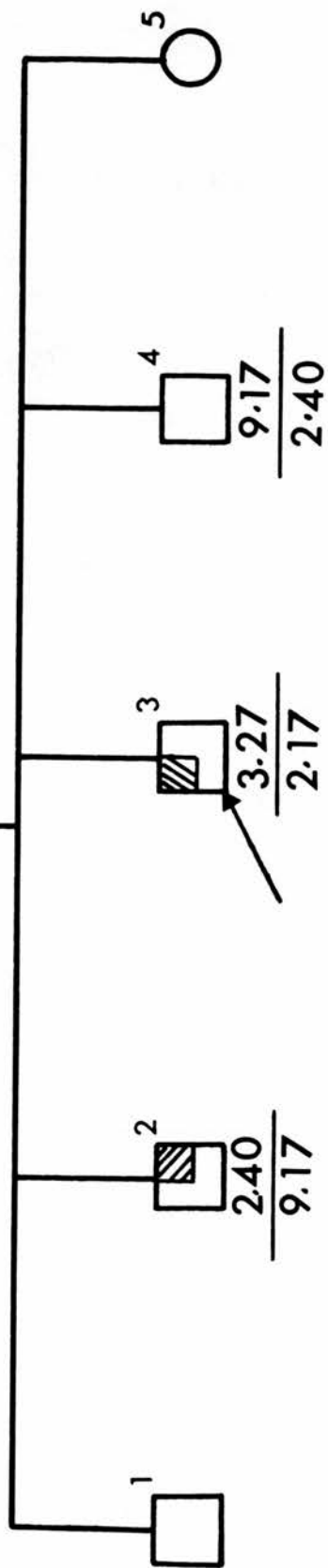


PEDIGREE P.31

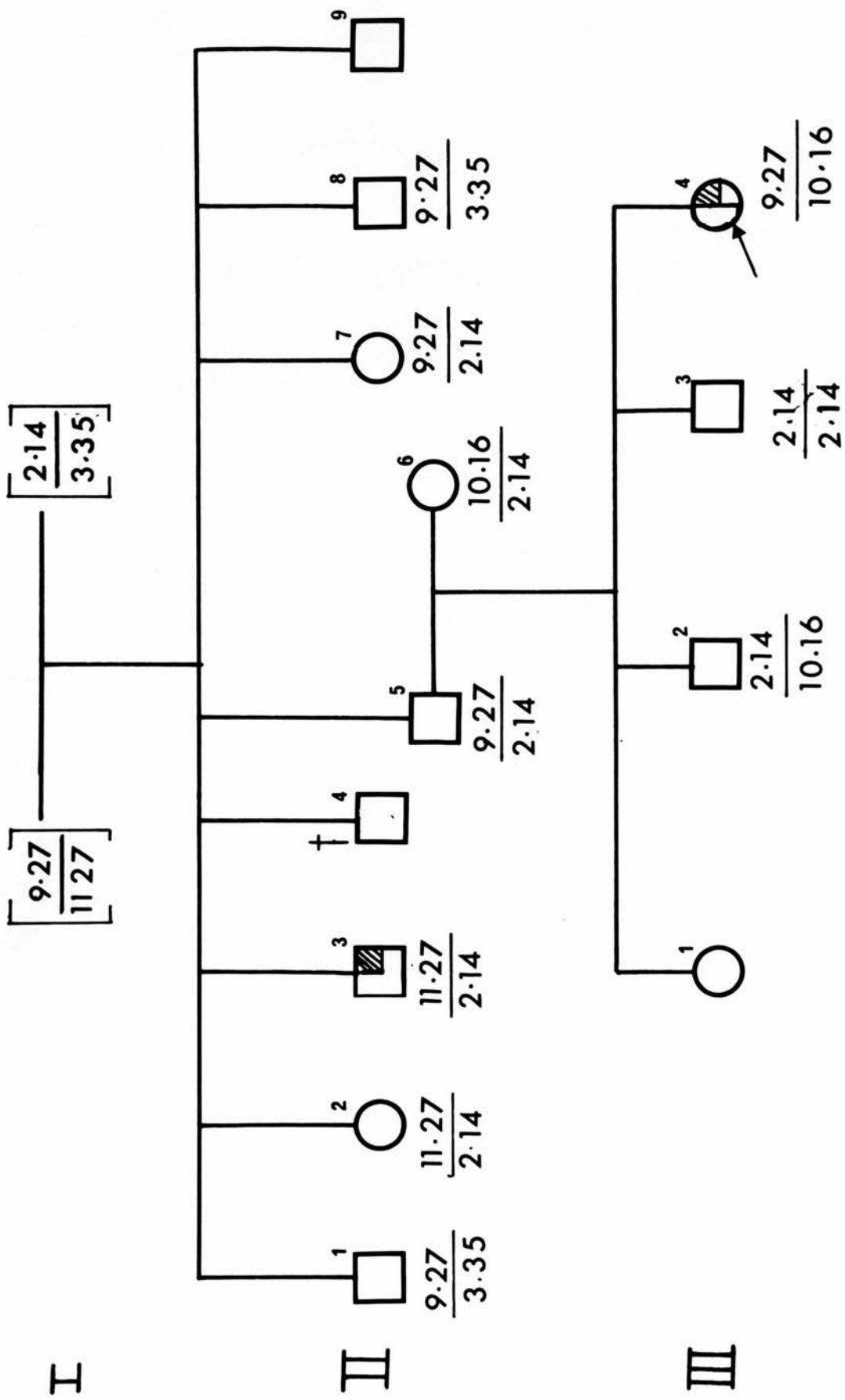
I



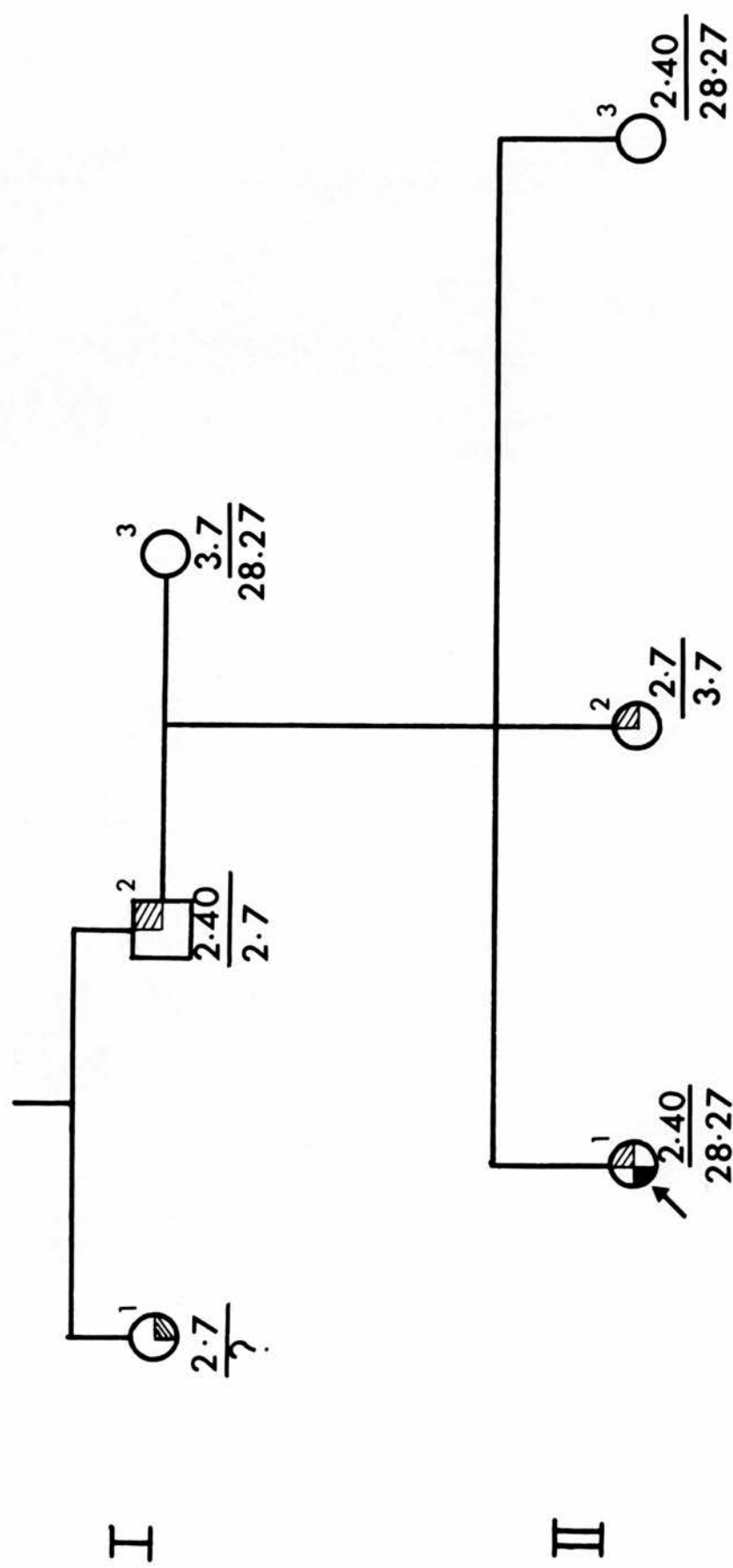
II



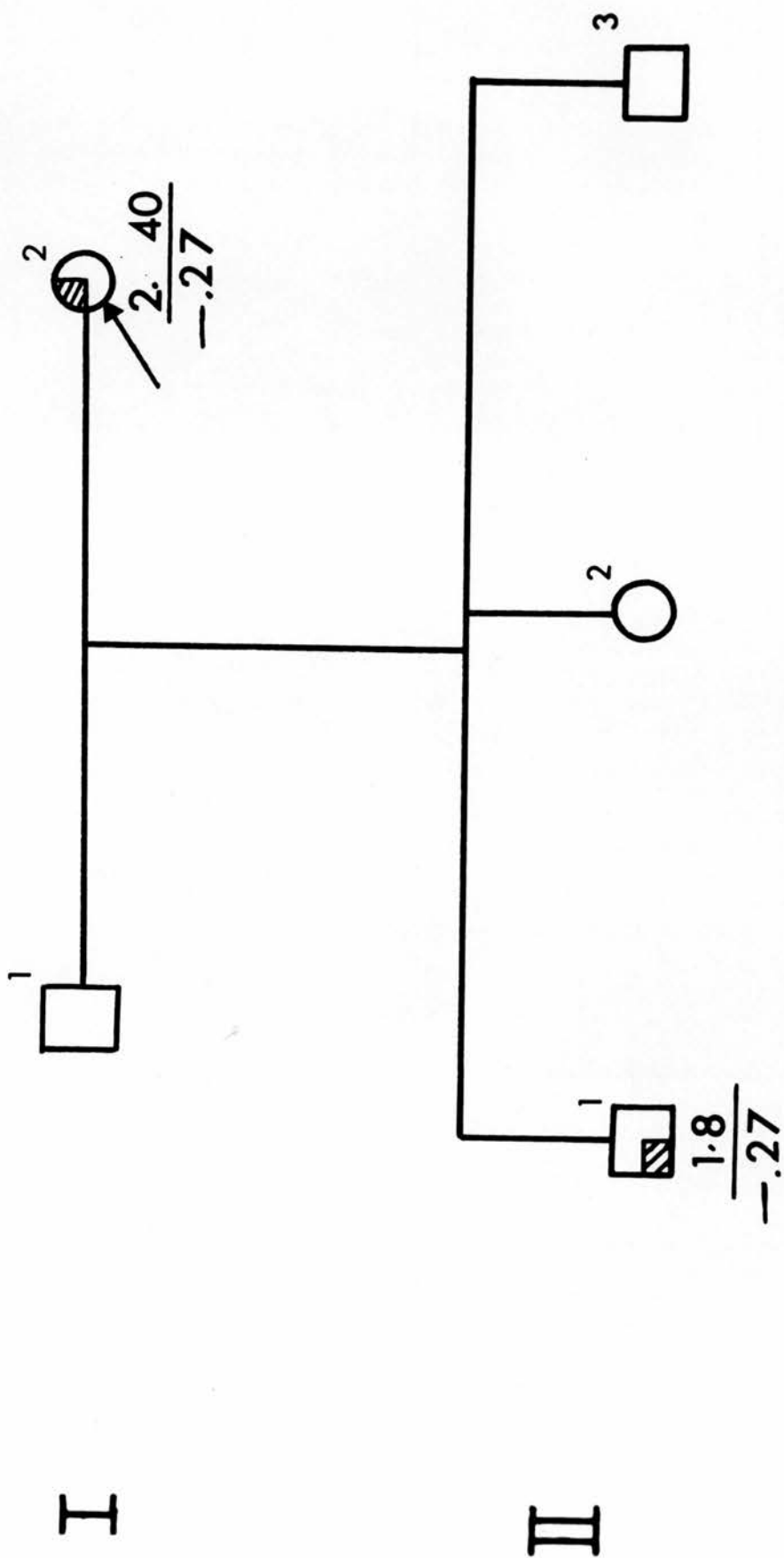
PEDIGREE P.32



PEDIGREE P.33



PEDIGREE P.34



4.6.5 Families with a person with an acute anterior uveitis and a relative with a related condition

(a) Monarthrititis

A family (Pedigree P.34) was seen in which the proband (I_2) with acute anterior uveitis alone had a 26 year old son with symptoms of a plantar fasciitis and Achilles tendonitis but with no back symptoms and radiologically normal sacroiliac joints.

(b) Ankylosing spondylitis

(See 4.6.2(f))

(c) Ankylosing spondylitis with inflammatory bowel disease

One family (Pedigree P.25) was seen in which the proband (II_1) with ulcerative colitis and ankylosing spondylitis had a younger sister (II_3) with acute anterior uveitis. Neither person was HLA-B27 positive but they had the same haplotype AW28,B8 in common.

4.6.6 Informative families with twins

Three families were seen each containing a pair of identical twins in which one of the pairs had ankylosing spondylitis. The results of multiple red blood cell grouping is shown in Table 4.27 and confirms a high probability of monozygosity for all these twin pairs. Each twin was shown to be HLA identical with his twin (Pedigrees P.35, P.36 and P.10).

In the first family (Pedigree P.35) the proband (II_1) aged 52 years developed symptoms of ankylosing spondylitis at the age of 23 years (Figure 4.15).

Table 4.27 Ages and details of multiple red blood cell grouping in three pairs of twins with ankylosing spondylitis together with the estimated probability of monozygosity (Race and Sanger, 1975).

Pedigree number	P.10		P.35		P.36	
Age at examination (years)	59		52		45	
Red blood cell groups tested	Red blood group type	Probability of dizygosity	Red blood group type	Probability of dizygosity	Red blood group type	Probability of dizygosity
ABO	O	0.6891	B	0.6945	A	0.6945
Rhesus	CcDee(R ¹ r)	0.5400	Dce(R ¹ R ¹)	0.5021	(R ¹ R ¹)	0.5021
MNS	MMSS	0.4176	MMSS	0.3888	MN ⁻	0.4733
P	P ₁	0.8489	P ₁	0.8489	P ₁	0.8489
Kell	K+	0.5394	K-	0.9548	K+	0.5394
Duffy	Fy(a+b+)	0.6219	Fy(a+b+)	0.6219	Fy(a+b-)	0.5047
Kidd	Jk(a+b-)	0.5732	Jk(a+b-)	0.5732	Jk(a+b-)	0.5732
Lutheran	Lu(a-b+)	0.9614	NT	-	NT	-
General probability of dizygosity		2.3333		2.3333		2.3333
Probability of liked sex being dizygotic		0.5000		0.5000		0.5000
Total relative chance of dizygosity (pD)		0.02845		0.0457		0.02551

Table 4.27 (Cont'd)

Total chance of dizygosity pD/1+pD)		0.02767		0.0437		0.02488
Total chance of monozygosity 1/(1+pD)		0.9723		0.9563		0.9757

NT - Not tested

PEDIGREE P.35

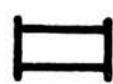
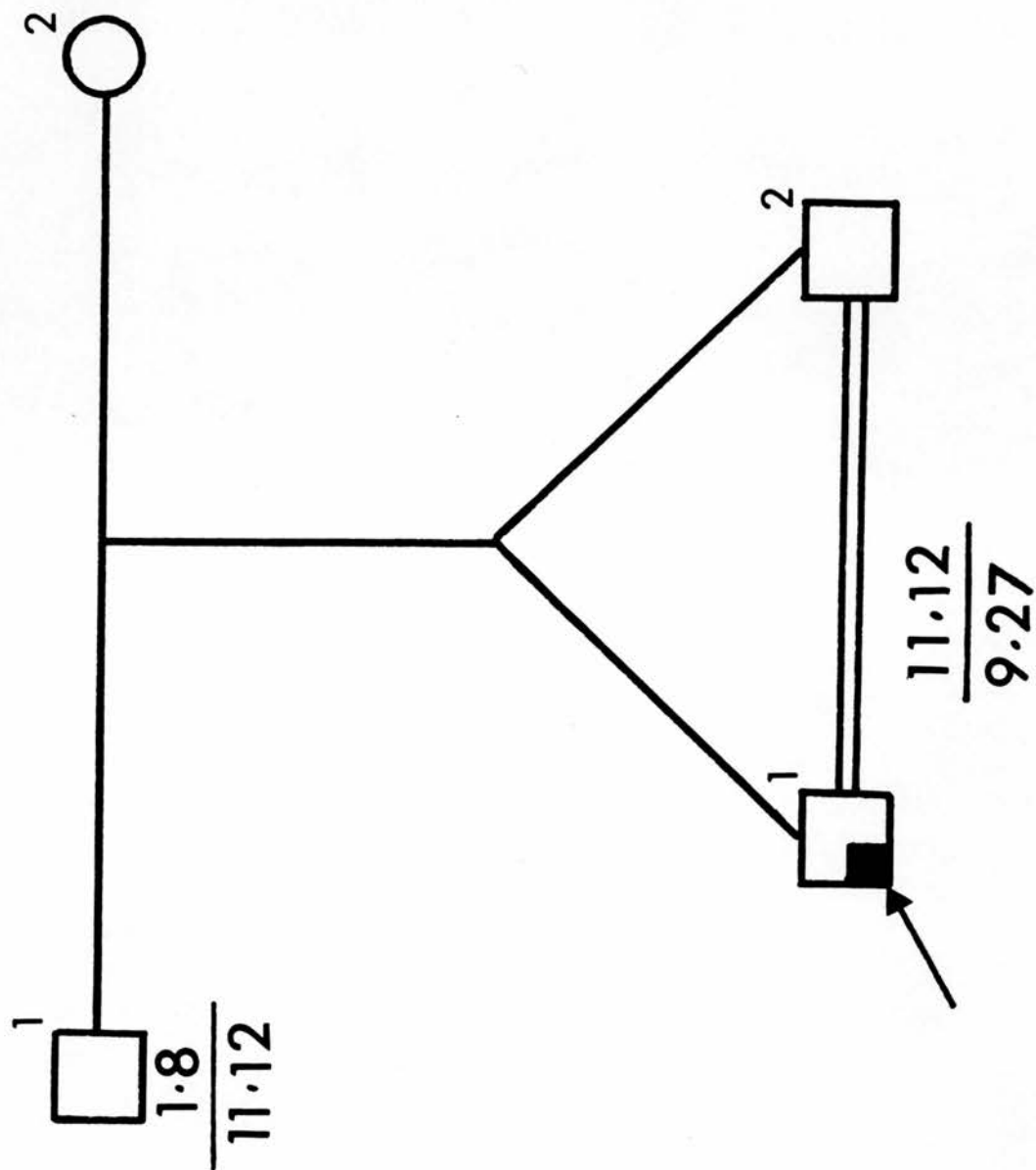


Figure 4.15 Grade 4 radiological sacroiliitis
in the proband of Pedigree P.35.

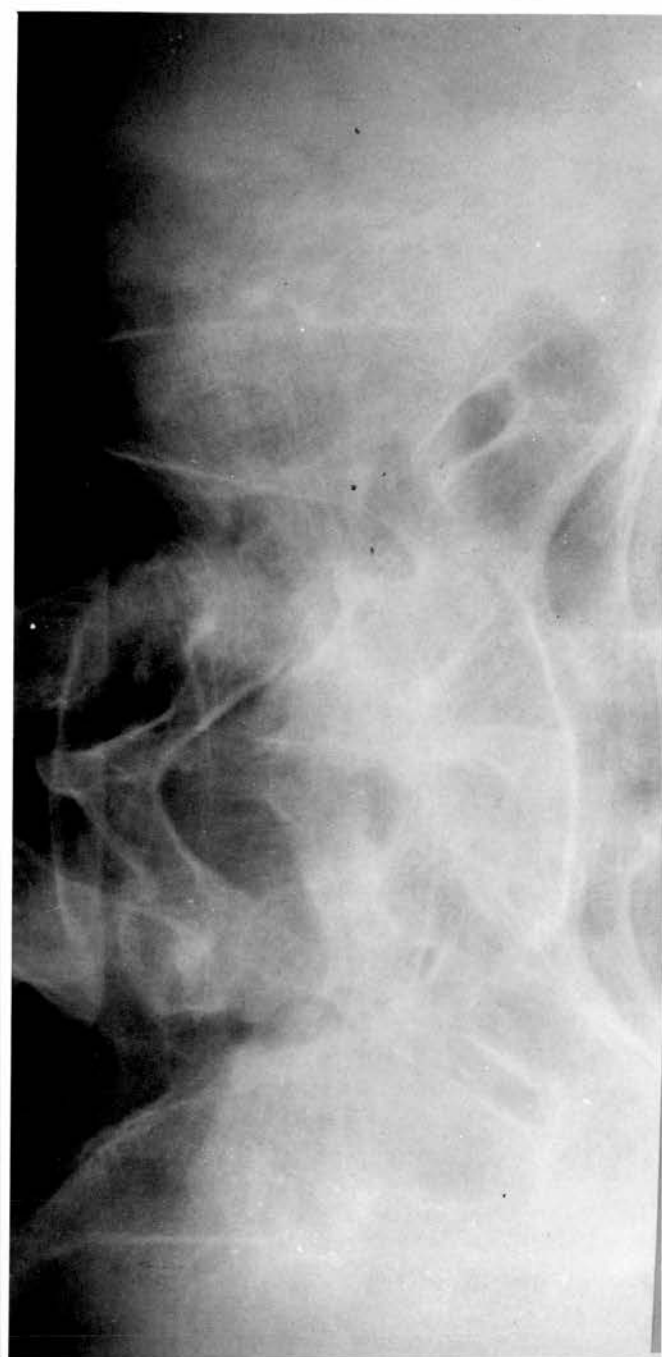


Figure 4.16 Radiologically normal sacroiliac joints of the identical twin of the proband of Pedigree P.35.



At the age of 32 years he left his home in Stratford-on-Avon and went to live in Liverpool. His identical twin brother had lived in Stratford-on-Avon all his life and was asymptomatic. Radiographs of his sacroiliac joints were normal (Figure 4.16). They were both HLA-B27 positive and HLA identical, having inherited their HLA-B27 haplotype from their deceased mother.

The second family (Pedigree P.36) was similar. The proband (II₁) aged 45 years had a 19 year history of ankylosing spondylitis (Figure 4.17). His identical twin brother was asymptomatic, had normal spinal movements and radiologically normal sacroiliac joints (Figure 4.18). They had lived in the same household until approximately 20 years previous.

The proband of the third family (Pedigree P.10) was a male aged 33 years (III₃) with a 15 year history of ankylosing spondylitis alone. His father (II₃) aged 59 years had a 32 year history of ankylosing spondylitis and when seen had a fixed lumbar spine and dorsal kyphosis. Radiographs showed fusion of the sacroiliac joints and posterior fusion in the lumbar spine (Figure 4.19). His identical twin brother (II₂) had had one episode of acute anterior uveitis but no back symptoms. His spinal movements were normal. Radiographs of his sacroiliac joints (Figure 4.20) showed a grade 3 bilateral sacroiliitis without changes in the lumbar spine. This twin had a daughter (III₁)

PEDIGREE P.36

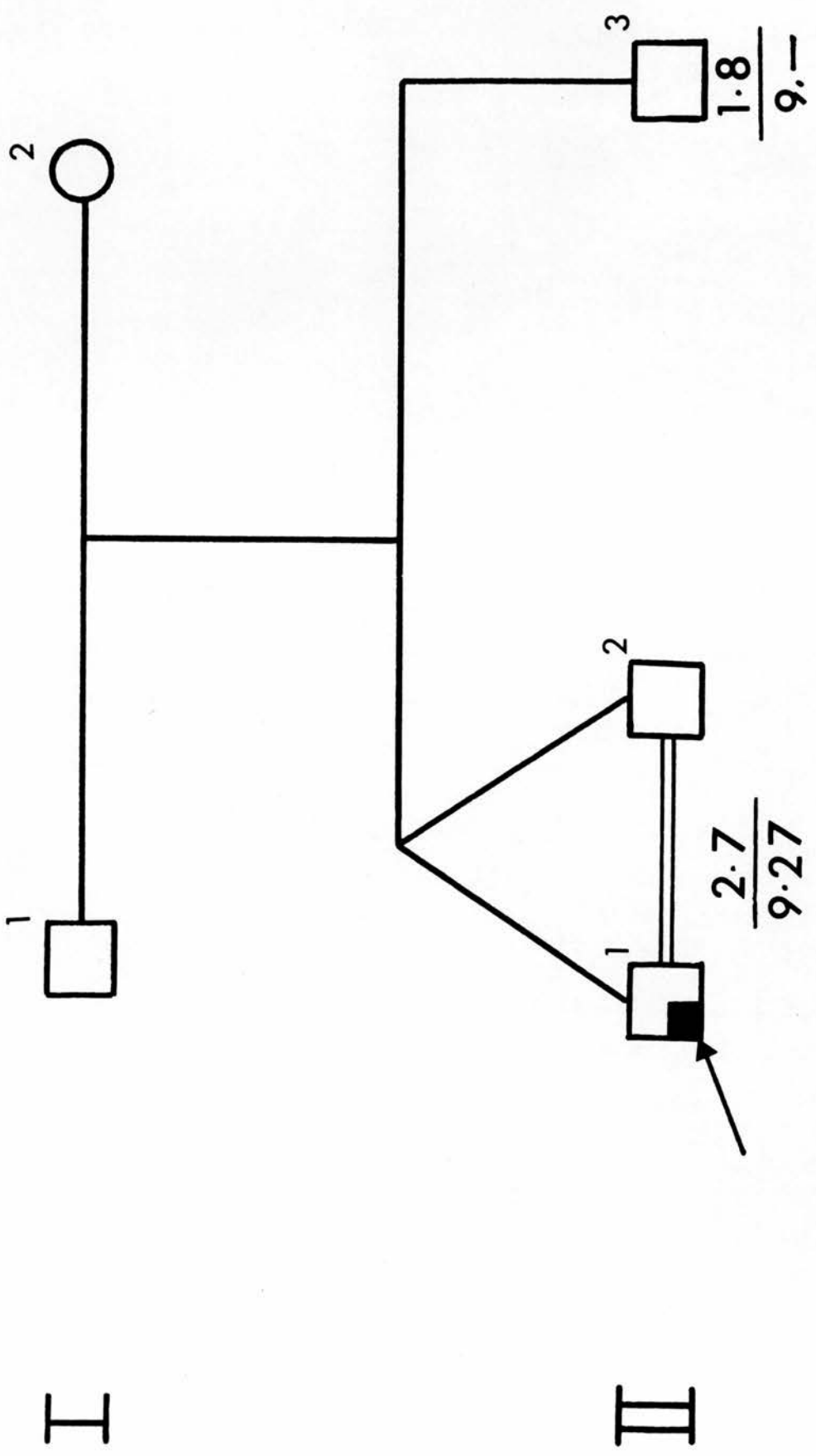
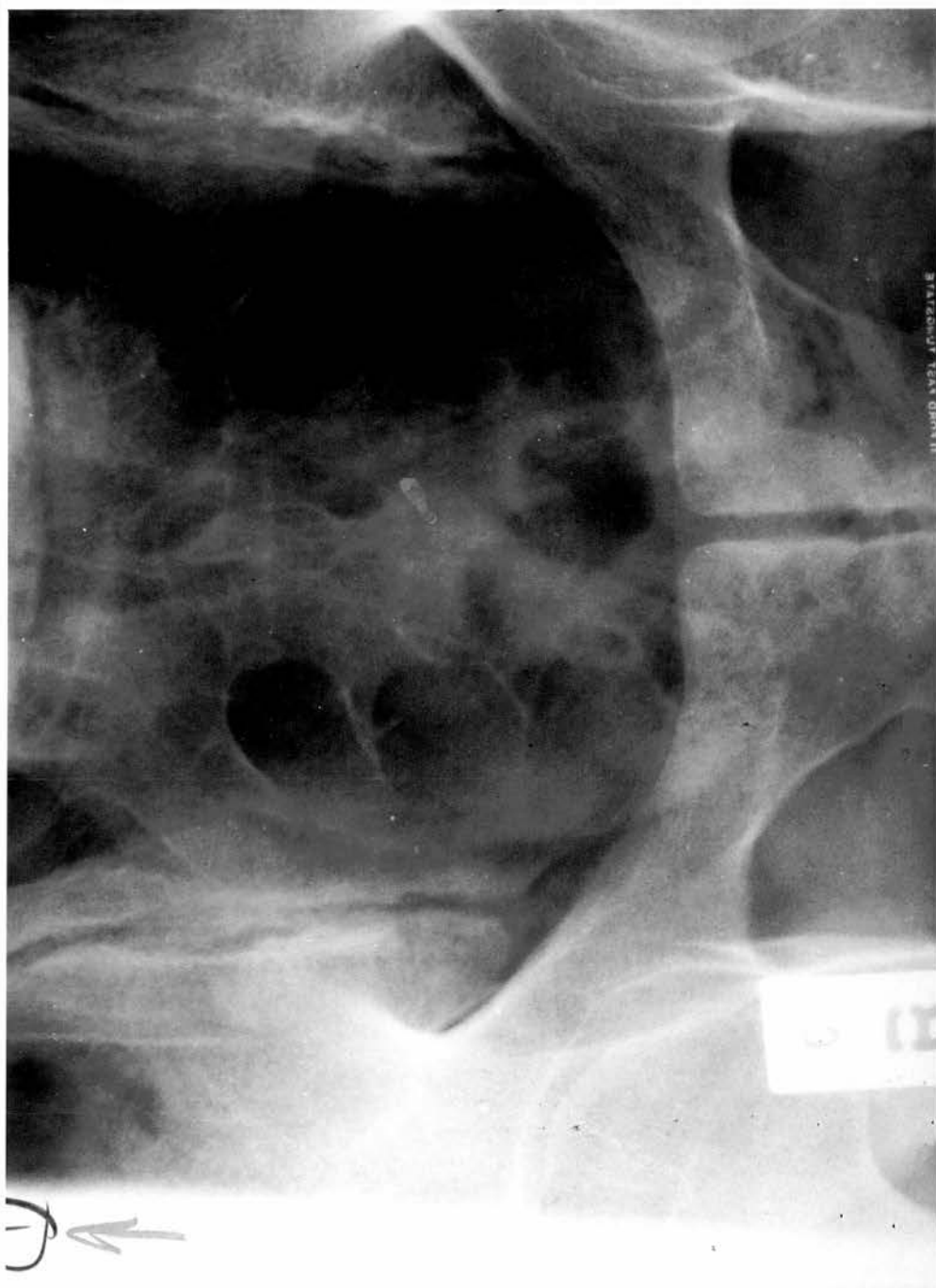


Figure 4.17 Bilateral grade 3 radiological
sacroiliitis in the proband of
Pedigree P.36.



Figure 4.18 Radiologically normal sacroiliac joints of the identical twin of the proband of Pedigree P.36.



PEDIGREE P.10

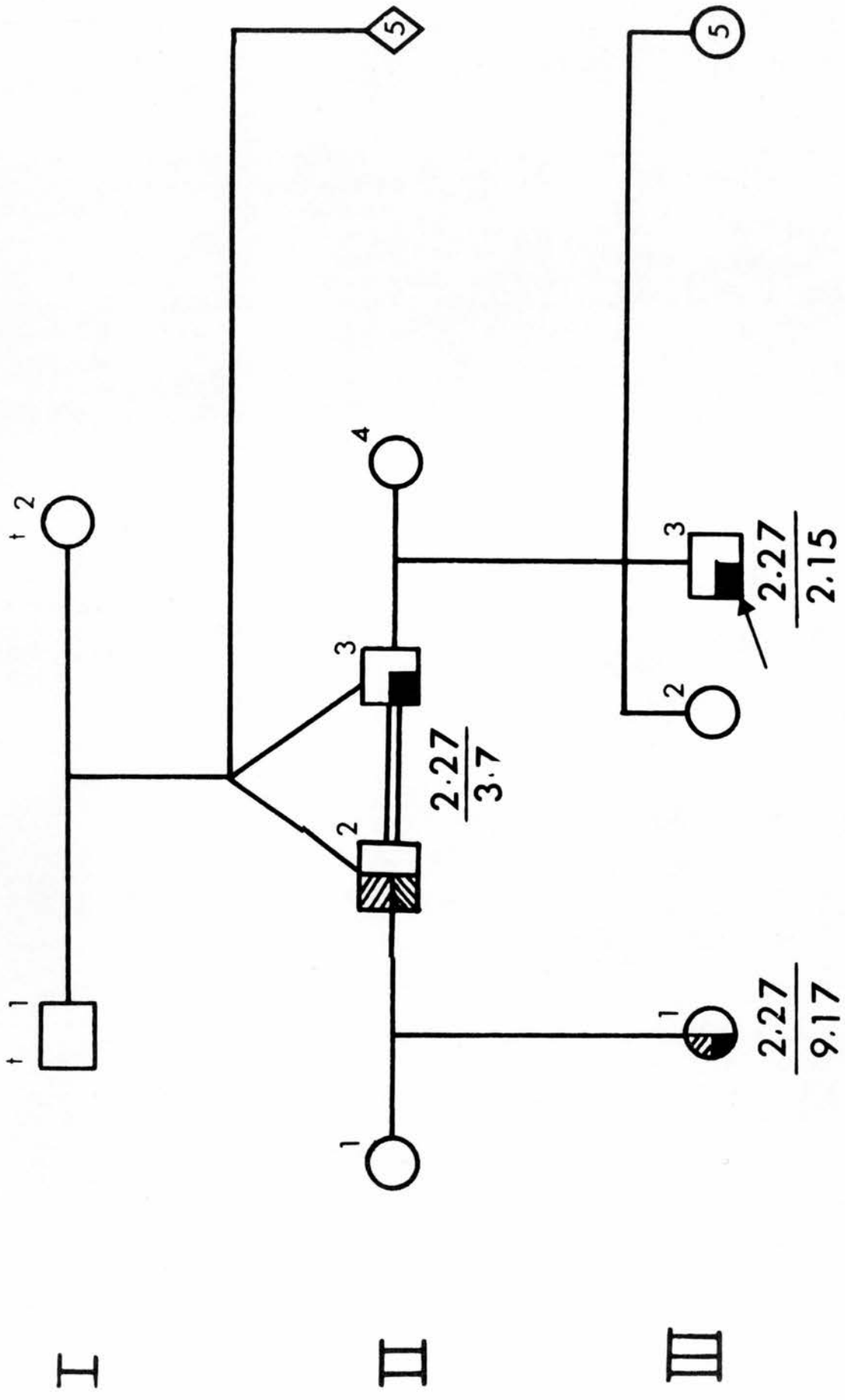


Figure 4.19 Radiological grade 4 sacroiliitis and 'bamboo spine' showing additional posterior fusion in the severely affected twin of Pedigree P.10.

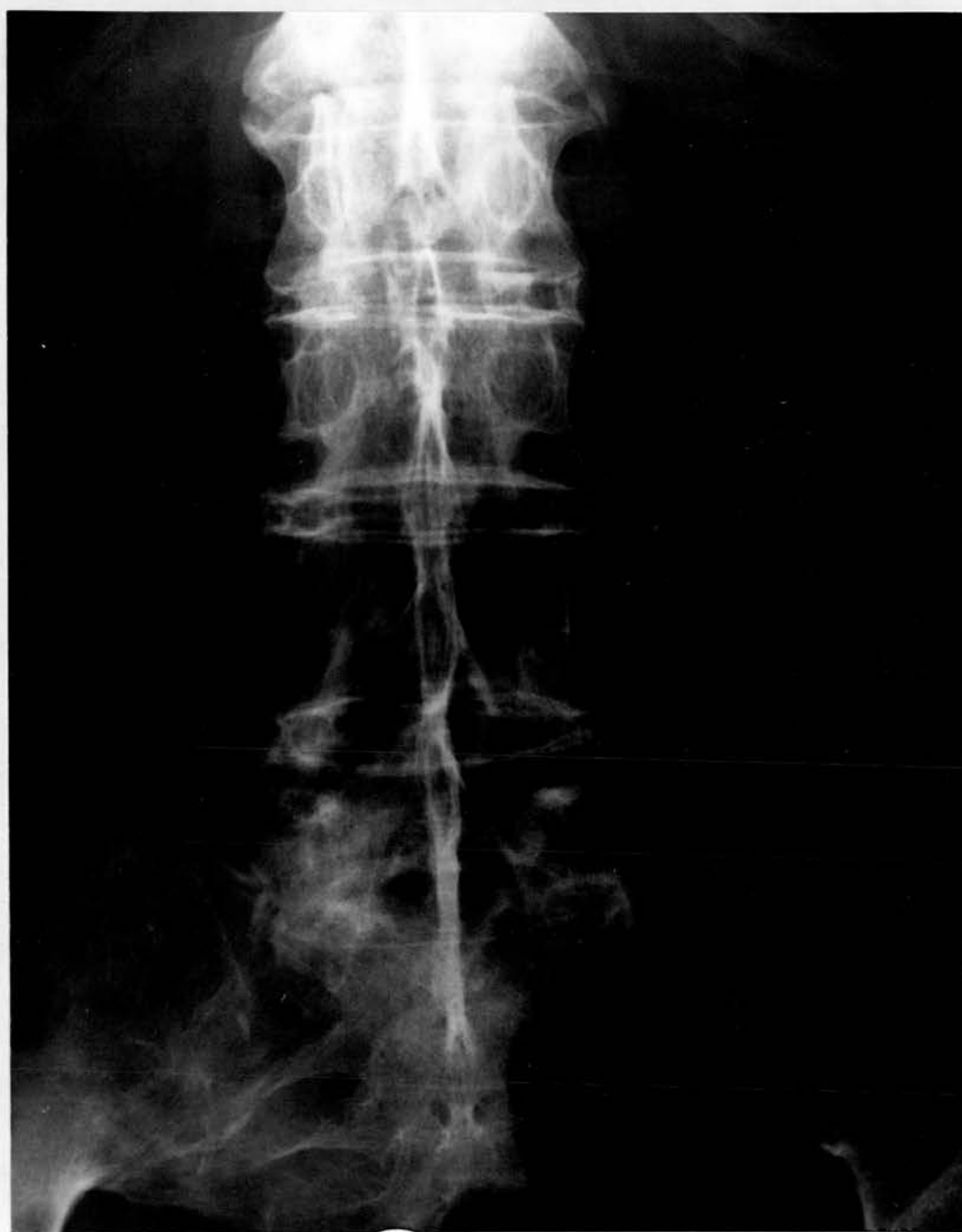


Figure 4.20 Bilateral grade 3 radiological sacroiliitis and normal spine in the identical twin of the severely affected twin of Pedigree P.10.



aged 33 years with a 15 year history of ankylosing spondylitis and radiologically bilateral grade 3 sacroiliitis. She had also had recurrent anterior uveitis since the age of 27 years.

4.6.7 Clinical, radiological and histocompatibility typing study of unselected parents of patients with ankylosing spondylitis alone

Two of the probands in this family study were female, the remaining 21 probands were male. All probands were HLA-B27 positive. Fourteen of the 23 fathers and twelve of the 23 mothers were HLA-B27 positive (Table 4.28). Three probands, all male were HLA-B27 homozygous. Four (28.6%) of the fourteen HLA-B27 positive fathers were found to have ankylosing spondylitis (Table 4.28). Three of these fathers had been previously diagnosed and this diagnosis was confirmed. One was asymptomatic but had restriction of all spinal movements and a chest expansion of 2 cm. Radiographs showed bilateral fusion of the sacroiliac joints and syndesmophytes in the lumbar spine (Figure 4.21). A further two (14.3%) asymptomatic HLA-B27 positive fathers with normal spinal movements and chest expansion were found to have bilateral grade 3 sacroiliitis (Figures 4.22 and 4.23).

No clinical or radiological disease was found in the HLA-B27 positive mothers nor in the HLA-B27 negative parents.

Table 4.28 Numbers of parents who had ankylosing spondylitis or radiological sacroiliitis from a total of 46 parents studied.

Parent	Number of parents	Number (percent) HLA-B27 positive	Number (percent) with ankylosing spondylitis	Number (percent) with radiological sacroiliitis
Fathers	23	14 (60.9%)	4 (28.6%)	2 (14.3%)
Mothers	23	12 (52.2%)	-	-

Figure 4.21 Bilateral grade 4 radiological sacroiliitis and 'bamboo spine' in an asymptomatic father of a proband with ankylosing spondylitis.



Figure 4.22 Bilateral grade 3 radiological
sacroiliitis in a father of a
proband with ankylosing spondylitis.



Figure 4.23 Bilateral grade 3 radiological
sacroiliitis in a father of a proband
with ankylosing spondylitis.



4.7 SERONEGATIVE OLIGOARTHRITIS

a A total of eighteen patients (14 male; 4 female) with a seronegative oligoarthritis alone predominantly affecting the weight bearing joints (Table 4.29) were seen during the course of the present study. The mean age of onset of this arthritis in the total group was 23.2 years (range 9 - 56 years), in the 14 males 23.7 years (range 11 - 56 years) and in the four females 17.6 years (range 9 - 22 years). All patients had normal radiographs of the sacroiliac joints.

4.7.1 Course of the arthritis

Opportunity for prolonged follow-up has not been possible. Four patients had continued intermittent symptoms from the affected joints. Ten patients were known to have become asymptomatic within twelve months from onset. The remaining five patients have not been seen more than twelve months after onset and when last seen have continued disease activity in their joints.

In three patients complete resolution of a previous similar episode was known to have occurred and they were seen with a subsequent recurrence. Two female patients had recurrences at three and four years respectively after the previous episode. One male had a recurrence thirteen years after the first episode having been totally asymptomatic in the intervening years.

4.7.2 Other related disorders

No patient had coincidental extra-articular symptoms to suggest Reiter's syndrome, psoriatic arthritis

Table 4.29 Frequencies of involvement of
individual peripheral joints in
18 patients with seronegative
oligoarthritis alone

Joints involved	Number of patients with each joint involved
Knees	17
Ankles	6
Back	4
Heels	3
Elbows	2
Metacarpophalangeal/ interphalangeal	2
Shoulders	1
Buttocks	1
Wrist	1
Toes	1

enteropathic synovitis. All patients were asked about recent sexual exposure and all denied extramarital contact. In the absence of symptoms of urethritis or other features to suggest Reiter's syndrome further urogenital enquiry and investigation was not routinely pursued.

2/ One male aged 13 years had a short diarrhoeal illness three weeks prior to the onset of swelling of both ankle joints. Culture of the stools was performed with negative findings and agglutinating antibodies to *Salmonellae* stains and *Yersinia enterocolitica* were absent.

One male aged 24 years was seen with Reiter's syndrome. He had a urethritis followed four days later by conjunctivitis, an ankle synovitis and mouth ulcers. He described a synovitis of the right knee two years previously. This episode had not been accompanied by any other features.

One year after a lower limb seronegative oligoarthritis which totally resolved, a 57 year old man developed his first episode of acute anterior uveitis.

One female at the age of 20 years had an acute anterior uveitis with full recovery and no other symptoms. Two years later she developed a lower limb seronegative oligoarthritis.

4.7.3 Family History

Two boys both aged 11 years had fathers with ankylosing spondylitis (Pedigrees P.28 and P.29). One

of these boys (Pedigree P.28) had a persistent synovitis of the left knee and backache. His sacroiliac joints were considered radiologically normal for his age. His father gave a long history of mild undiagnosed back pain and stiffness. Clinical and radiological examination confirmed definite ankylosing spondylitis.

The other boy (Pedigree P.29) had persistent discomfort in and around both heels. Both his father and paternal uncle were known to have ankylosing spondylitis.

No patient gave a family history of psoriasis, chronic inflammatory bowel disease or acute anterior uveitis.

4.7.4 Histocompatibility Testing

Histocompatibility typing was performed in all 18 patients. HLA-B27 was present in 77.8% of patients which compared with a frequency of 8.2% in 451 controls gives $\chi^2_c = 79.41$; $p = 5.1 \times 10^{-19}$ (Table 4.30).

This p value remains significant when multiplied by 24 to allow for the number of antigens tested ($p = 1.2 \times 10^{-17}$). The frequencies of HLA-B27 in males and females was similar.

(a) Patients with related disorders

The male patient with diarrhoea three weeks prior to the onset of his arthritis was HLA-B27 positive. The male who developed definite Reiter's syndrome after an asymptomatic period following full recovery from a synovitis of the right knee was HLA-B27 positive.

Table 4.30 HLA frequencies in patients with seronegative oligoarthritis alone and controls; Yates χ^2 and Woolf relative risk and χ^2 ($w\chi^2$)

HLA antigen	Patients with seronegative oligoarthritis (18)		Controls (451)		Yates χ^2	p	Relative risk χ	$w\chi^2$	p
	Number with antigen	Percent with antigen	Number with antigen	Percent with antigen					
A1	5	27.7	154	34.2	0.21	0.646	0.742	0.311	0.577
A2	11	61.1	197	43.7	1.48	0.222	2.047	2.113	0.146
A3	4	22.2	131	29.1	0.13	0.719	0.698	0.389	0.533
A9	3	16.7	88	19.5	0.09*	0.764	0.825	0.894	0.344
A10	2	11.1	40	8.9	0.11*	0.741	1.284	0.106	0.745
A11	2	11.1	58	12.9	0.05*	0.826	0.847	0.047	0.828
A28	2	11.1	24(397)	6.1	0.10	0.749	1.943	0.727	0.394
A29	0	-	31(408)	7.6	1.46*	0.226	0.324	1.170	0.279
AW30/31	1	5.6	23(396)	5.8	0.00*	1.000	0.954	0.002	0.964
AW32	1	5.6	26(404)	6.4	0.02*	0.881	0.855	0.222	0.638
A Blank	5	27.7	130	28.8	0.01*	0.920	0.950	0.009	0.924
B5	0	-	44	9.8	1.95*	0.162	0.247	1.810	0.179
B7	3	16.7	135	29.9	0.90	0.342	0.468	1.403	0.236
B8	4	22.2	128	28.4	0.09*	0.764	0.721	0.322	0.570
B12	3	16.7	128	28.4	0.67	0.412	0.505	1.138	0.286

Table 4.30 (Cont'd)

B13	0	-	23	5.1	0.99*	0.322	0.493	0.457	0.499
B14	2	11.1	33	7.3	0.02	0.889	1.583	0.355	0.551
BW15	1	5.6	45	10.0	0.05	0.834	0.531	0.370	0.543
BW17	0	-	38	8.4	1.70*	0.190	0.290	1.416	0.234
B18	0	-	25	5.5	1.10*	0.194	0.879	0.015	0.903
BW22	0	-	25	5.5	1.10*	0.194	0.879	0.015	0.903
B27	14	77.8	37	8.2	79.41	5.1×10^{-19}	39.162	38.339	6.0×10^{-10}
BW35	2	11.1	54	12.0	0.01*	0.912	0.919	0.012	0.913
BW37	0	-	5(141)	3.6	0.71	0.401	0.671	0.130	0.718
BW40	2	11.1	51	11.3	0.00*	1.00	0.980	0.001	0.975
B Blank	5	27.7	133	29.5	0.02	0.873	0.920	0.024	0.877

* uncorrected χ^2 used as Yates correction would result in overcorrection.

Both patients who had had acute anterior uveitis were HLA-B27 positive.

(b) Patients with recurrent disease

All three patients with a recurrence of a seronegative oligoarthritis were HLA-B27 positive.

(c) Family history

K Both boys with fathers with ankylosing spondylitis were HLA-B27 positive and had inherited the ^{same} HLA-B27 haplotype as their fathers (Pedigrees P.28 and P.29).

CHAPTER 5

DISCUSSION OF RESULTS

5.1 ANKYLOSING SPONDYLITIS

5.1.1 Clinical Features

The present series of 119 patients with ankylosing spondylitis is clinically similar to previously reported series (Forrestier, Jacqueline and Rotes, 1949; Parr, White and Shipton, 1951; Hart and MacLagan, 1955; Wilkinson and Bywaters, 1958). The mean age of onset in these series was approximately 27 years compared with 25.6 years in the present series, 11% of patients having an onset of symptoms after the age of 40 years in both these earlier and present studies.

The sex ratio is variable, Parr, White and Shipton (1951) found a 5 to 4 male to female ratio whereas the later studies found a ratio of 9 to 1 (Hart and MacLagan, 1955) and 8 to 1 (Wilkinson and Bywaters, 1958) compared with 8.7 to 1 in the present series.

Peripheral arthritis has been noted to be common. The 38.7% frequency in the present series is considerably less than the 63% frequency noted by Wilkinson and Bywaters (1958). The distribution, however, is similar to that found in these previous series affecting predominantly the lower limb large weight bearing joints. These joints have also been noted previously to be the site of onset of this arthritis in between 6 and 19% of patients compared with the 10.9% of patients in the present series having such an onset.

In their series of 222 patients Wilkinson and Bywaters (1958) saw two who probably also had rheumatoid

arthritis, compared with the one patient with this condition in the present series. It has recently been suggested that rheumatoid arthritis and ankylosing spondylitis are positively associated together (Fallet et al, 1977). The prevalence of rheumatoid arthritis in ankylosing spondylitis in the present series and that of Wilkinson and Bywaters (1958) is in keeping with that expected from a population prevalence of rheumatoid arthritis of 1% of males. Fallet et al (1977) do not state from what size of population their 10 cases of rheumatoid arthritis and ankylosing spondylitis were derived. It should be noted that they are derived from three major centres, Geneva, London and Oxford. They have calculated that the population necessary to produce these 10 cases by the chance association of the two diseases would be between 500,000 and 2,000,000. This is not excessively large when considering the combined population of these three cities which is 7,795,078 (Pears Cyclopaedia, 1977). Luthra, Ferguson and Conn (1976) have also reported two patients with both diseases and considered them to be examples of coincidental disease.

Wilkinson and Bywaters (1958) did not find any examples of Reiter's syndrome though four (1.8%) of their patients did have urethritis and peripheral arthritis compared with two definite cases and one possible case of Reiter's syndrome seen in the present series.

The 14.3% frequency of acute anterior uveitis is similar to the previously reported frequencies of

between 4% and 25%.

Aortic regurgitation was found in two (0.9%) of Wilkinson and Bywaters (1958) patients compared with the one (0.8%) in the present series.

5.1.2 Histocompatibility Testing

The high frequency of HLA-B27 in patients with ankylosing spondylitis is confirmed in the present series. The details of this series and eleven others in which more than 50 caucasian patients were tested are shown in Table 5.1. The relative risk (Haldane, 1955) for the twelve series combined is 66.82 (95% confidence limits 52.43 - 85.12) and the total χ^2 (1 d.f.) is 1161.37 for which p approximates to zero. There is probably some heterogeneity in the estimates of the natural logarithm (y) of the relative risk between these studies, the χ^2 for heterogeneity of the y's being 22.77 (11 d.f.) for which $p < 0.02$. Whilst patients with related conditions such as psoriasis and inflammatory bowel disease have been excluded from later series the authors of some do not state that such exclusions were specifically made. To exclude these conditions is important as will be discussed later (see 6.4). In addition standard criteria have not always been applied. The present study and Gomor, Gyodi and Bakos (1977) used the New York criteria (Bennett and Wood, 1968) for ankylosing spondylitis, whereas Brewerton et al (1973a) and Russel et al (1974) used more stringent criteria most patients having advanced disease. Others

Table 5.1 Combined analysis of HLA-B27 frequencies in 11 series of caucasoids with ankylosing spondylitis.

Series	Number of patients	Number of controls	Percent patients HLA-B27 positive	Percent controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1973a)	75	75	96.0	4.0	429.08	6.062	1.896	11.494	69.677
Schlossstein et al (1973)	40	906	87.5	8.0	90.80	4.509	4.121	18.582	83.784
Amor et al (1974)	53	152	81.1	4.0	93.37	4.537	3.798	17.232	78.179
Sachs et al (1975)	67	174	94.0	9.8	127.00	4.844	3.603	17.453	84.542
Moller et al (1975)	126	100	85.7	12.0	41.52	3.726	6.668	24.845	92.572
Truong et al (1975)	50	478	94.0	4.8	263.06	5.572	3.178	17.708	98.668
Russell et al (1974)	50	295	90.0	9.2	80.77	4.392	4.389	19.276	84.662
Berg-Loonen et al (1977)	118	778	81.4	9.9	38.82	3.659	14.699	53.784	196.794
Gomor, Gyodi and Bakos (1977)	55	352	92.7	12.8	77.34	4.348	4.095	17.805	77.416
Huau et al (1977)	108	250	80.6	8.4	43.44	3.771	9.379	35.368	133.374
Present series	119	451	87.4	8.2	74.52	4.311	9.926	42.791	184.472

$Y = \sum wy / \sum w = 4.202$ (95% confidence limits = 3.960 and 4.444)

$x = \text{Antilog}_e Y = 66.82$ (95% confidence limits = 52.43 and 85.12)

χ^2 for significance of $Y = Y^2 \sum w = 1161.37$, for 1 d.f. $p \sim 0.00$

χ^2 for heterogeneity of y's = $\sum wy^2 - Y^2 \sum w = 22.77$, for 11 d.f. $p < 0.02$

(Schlosstein et al, 1973; Sachs et al, 1975; Truong et al, 1975) do not state their specific criteria. The Rome criteria (Jeffrey, Ball and Kellgren, 1963) allow the diagnosis of ankylosing spondylitis on clinical grounds alone in the absence of radiological sacroiliitis. Moll and Wright (1973c) favour a modification of the New York criteria in which numerical weight is given to each criteria, radiological sacroiliitis being weighted higher than each of the clinical criteria. This reflects the importance that is placed on this radiological sign in ordinary clinical practice, minor radiological changes in the presence of suggestive symptoms being sufficient for a tentative diagnosis to be made. It is therefore possible that some series have only included patients with the most severe, advanced and obvious disease, whereas others have included patients who would not satisfy the now largely accepted New York criteria but where diagnostic features would be included by the less stringent Rome criteria. If this is the case then this could be a further source of heterogeneity with respect to the individual values for the relative risk (x) and its natural logarithm (y).

Van der Linden et al (1977) found no difference in the frequency of HLA-B27 in patients with and without episodes of peripheral arthritis and the overall result in this present study is in agreement with their findings. Patients with dactylitis of the toes, however, were found in the present study to have a significantly lower frequency of HLA-B27 compared with patients who did not

have this type of peripheral arthritis ($p = 0.01$). In a separate study of nine patients with dactylitis of the toes who did not have ankylosing spondylitis or radiological sacroiliitis Ceulaer, van der Linden and Cats (1977) found all nine to be HLA-B27 positive. They do not state whether other diseases, in particular psoriasis, were excluded. It is difficult to reconcile this disparity in findings at present but study of larger groups of patients with dactylitis with and without ankylosing spondylitis would be useful.

The frequency of HLA-B27 in patients with and without acute non-granulomatous anterior uveitis has been found to be similar confirming the findings of Van der Linden et al (1977). It is interesting to note that all patients with recurrent uveitis were HLA-B27 positive, and it is possible that the risk of recurrence is higher in HLA-B27 positive patients with ankylosing spondylitis. In their study of ninety patients with acute non-granulomatous anterior uveitis Mapstone and Woodrow (1975) also found HLA-B27 to be more frequent in those patients with a previous episode irrespective of the presence or absence of ankylosing spondylitis.

Clinical severity of the disease was not assessed in the present study, though it was noted that several of the HLA-B27 negative patients did have clinically severe disease with regard to the presence of spinal rigidity and deformity and the difficulties that ensued from this. Others have also found the clinical severity

to be independant of the presence or absence of HLA-B27 (Brautbar et al, 1977; van der Linden et al, 1977). Russell, Lentle and Schlaut (1976) claimed more severe radiological disease in HLA-B27 positive patients than HLA-B27 negative patients. Statistical analysis of their data, however, fails to show any significant differences (Table 5.2). Van der Linden et al (1977) found equally severe radiological changes in HLA-B27 positive and negative patients. In the present series the radiological severity of sacroiliitis was not significantly different in patients with and without HLA-B27. The results of the present study do not suggest that the type of syndesmophyte present in the spine is related to the presence or absence of HLA-B27.

Van der Linden et al (1977) found no difference in the age of onset of symptoms between HLA-B27 positive and negative patients. Brautbar et al (1977) has stated that the age of onset is later in HLA-B27 negative patients compared with HLA-B27 positive patients and Van den Berg-Loonen et al (1977) found a significantly higher frequency of HLA-B27 in patients with an onset of symptoms before 45 years than in those with an onset after that age. The present study, by finding a significantly lower age of onset in HLA-B27 positive patients than HLA-B27 negative patients confirm the results of these latter two studies.

Although not conclusive these studies suggest that HLA-B27 negative patients have a later age of onset of

Table 5.2 A statistical analysis of the radiological comparison of HLA-B27 positive and negative patients with ankylosing spondylitis reported by Russel, Lentle and Schlaut (1976)

HLA typing	Radiological grade of sacroiliitis		
	2	3	4
HLA-B27 negative	3	12	2
HLA-B27 positive	1	11	4

$$\chi^2 (2 \text{ d.f.}) = 1.63 \quad p > 0.30$$

HLA typing	Number of patients	
	with radiological changes outwith the pelvis	without radiological changes outwith the pelvis
HLA-B27 negative	2	15
HLA-B27 positive	6	10

$$\chi^2_c = 1.70 (1 \text{ d.f.}) \quad p > 0.10$$

ankylosing spondylitis than their HLA-B27 positive counterparts and that if they develop acute anterior uveitis it is less likely to become recurrent. The severity of their spinal disease, however, is not likely to differ.

5.2 INFLAMMATORY BOWEL DISEASE WITH ANKYLOSING SPONDYLITIS OR RADIOLOGICAL SACROILIITIS

5.2.1 Clinical Features

In the eleven patients in the present series with both chronic inflammatory bowel disease and ankylosing spondylitis patients have been seen in whom the onset of either disease preceded the other by several years. This has been noted by others (Ansell and Wigley, 1964; Dekker-Saeys et al, 1978a).

Five of these eleven patients had a history of acute anterior uveitis which is similar to the 50% frequency found by Wright et al (1965) but somewhat higher than the 20% frequency found by Dekker-Saeys et al (1978a). Ansell and Wigley found psoriasis in 6% of patients with Crohn's disease, compared with a 1 - 2% prevalence in the general population (Ingram, 1954). No similar patient was seen in the present series but this is probably the result of studying only a small number of patients.

5.2.2 Histocompatibility Testing

The high frequency (63.6%) of HLA-B27 in patients with both chronic inflammatory bowel disease and ankylosing spondylitis compared with controls (8.2%) is

in agreement with other similar published series (Table 5.3). A combined analysis of these seven series gives an overall relative risk (x) of 17.4 for which χ^2 is 207.58 (1 d.f) and $p = 4.84 \times 10^{-47}$ confirming a highly significant association between the combination of these diseases and HLA-B27. There is little or no heterogeneity between the series ($p > 0.5$), but since the relative risk of 4.3 found by Nagant de Deuxchaisnes et al (1974) in their series of patients with Crohn's disease and ankylosing spondylitis was so much lower than that of 33.6 found by Brewerton et al (1974) in a series of patients with ulcerative colitis and ankylosing spondylitis, the combined analysis has been repeated for both ulcerative colitis (Table 5.4) and Crohn's disease (Table 5.5) alone with ankylosing spondylitis. For patients with ulcerative colitis and ankylosing spondylitis the combined relative risk (x) is 24.4 with 95% confidence limits of 12.4 and 47.5, and for Crohn's disease with ankylosing spondylitis the combined relative risk (x) is 9.8 with 95% confidence limits of 5.8 and 16.5. It can be seen that the upper 95% confidence limit for the relative risk (x) for patients with Crohn's disease and ankylosing spondylitis is within the lower 95% confidence limit of the relative risk (x) for patients with ulcerative colitis and ankylosing spondylitis. This indicates that there is no statistical evidence that the relative risk for HLA-B27 differs with the type of chronic inflammatory bowel disease. The total number of patients included in this separate analysis of Crohn's

Table 5.3 Combined analysis of HLA-B27 frequencies in 7 series of caucasoids with chronic inflammatory bowel disease and ankylosing spondylitis.

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1974) ⁺	18	300	72.2	6.6	33.59	3.514	3.457	12.148	42.687
Nagant de Deuxchaînes et al (1974)*	11	200	27.3	8.5	4.32	1.463	2.369	5.778	14.093
Bluestone et al (1975)*	12	254	66.7	5.9	29.19	3.374	2.647	8.931	30.134
Deshayes et al (1976)*	6	134	66.7	6.0	26.79	3.288	1.533	5.042	16.573
Mallas et al (1976)*	7	283	71.4	6.7	29.84	3.396	1.806	6.132	20.826
Dekker-Saeys et al (1978b)*	50	778	56.0	9.9	11.47	2.439	10.845	26.452	64.516
Present series*	11	451	63.6	8.2	18.422	2.914	2.827	8.238	24.006

Nature of chronic inflammatory bowel disease in series:

⁺ - ulcerative colitis; * - Crohn's disease; * - ulcerative colitis or Crohn's disease

$$Y = \sum wy / \sum w = 2.854 \text{ (95\% confidence limits = 2.656 and 3.052)}$$

$$x = \text{Antilog } Y = 17.36 \text{ (95\% confidence limits = 14.24 and 21.16)}$$

$$\chi^2 \text{ for significance of } Y = Y^2 \cdot \sum w = 207.58, \text{ for 1 d.f. } p = 4.84 \times 10^{-47}$$

$$\chi^2 \text{ for heterogeneity of } y's = \sum wy^2 - Y^2 \cdot \sum w = 5.26, \text{ for 6 d.f. } p > 0.50$$

Table 5.4 Combined analysis of HLA-B27 frequencies in 3 series of caucasoids with ulcerative colitis and ankylosing spondylitis.

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1974)	18	300	72.2	6.6	33.59	3.514	3.457	12.148	42.687
Dekker-Saeys et al (1978b)	12	778	66.7	9.9	17.10	2.839	3.074	8.726	24.773
Present series	7	451	71.4	8.2	24.32	3.191	1.891	6.035	19.259

$Y = \sum wy / \sum w = 3.195$ (95% confidence limits = 2.520 and 3.870)
 $x = \text{Antilog}_e Y = 24.40$ (95% confidence limits = 12.43 and 47.47)
 χ^2 for significance of $Y = Y^2 \cdot \sum w = 85.98$, for 1 d.f. $p = 1.8 \times 10^{-20}$
 χ^2 for heterogeneity of y's = $\sum wy^2 - Y^2 \cdot \sum w = 0.742$, for 2 d.f. $p > 0.70$

Table 5.5 Combined analysis of HLA-B27 frequencies in 4 series of caucasoids with Crohn's disease and ankylosing spondylitis

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Nagaut de Deuxchaisnes et al (1974)	11	200	27.3	8.5	4.32	1.463	2.369	3.466	5.071
Deshayes et al (1976)	6	134	66.7	6.0	26.79	3.288	1.533	5.040	16.573
Dekker-Saeys et al (1978b)	38	778	52.6	9.9	10.03	2.306	8.734	20.141	46.444
Present series	4	451	50.0	8.2	11.05	2.403	1.438	3.456	8.304

$Y = \sum wy / \sum w = 2.281$ (95% confidence limits = 1.759 and 2.803)

$x = \text{Antilog } Y = 9.79$ (95% confidence limits = 5.81 and 16.49)

χ^2 for significance of $Y = Y^2 \cdot \sum w = 73.23$, for 1 d.f. $p = 1.2 \times 10^{-17}$

χ^2 for heterogeneity of y 's = $\sum wy^2 - Y^2 \cdot \sum w = 3.17$, for 3 d.f. $p > 0.30$

disease and ulcerative colitis is only 96 which is relatively small for this type of analysis. It would be wise, therefore, in future studies to separate patients with Crohn's disease from those with ulcerative colitis so far as this is possible in the analysis of the results in order that further comparisons may be made. This is also important as although four large series of patients with Crohn's disease and ulcerative colitis (Jacoby and Jayson, 1974; Deshayes et al, 1976; Hyla, Franck and Davis, 1976; Huaux et al, 1977) have not shown an increased frequency of HLA-B27 in patients with bowel disease alone others have found an increased frequency of HLA-B27 in Crohn's disease (Russel et al, 1974) and still others in ulcerative colitis (Mallas et al, 1976; Van den Berg-Loonen et al, 1977). Such an increased frequency of HLA-B27 in one of these chronic inflammatory bowel diseases and not the others could affect the degree of association with HLA-B27 and hence the relative risk (x) when ankylosing spondylitis is also present.

Only two patients were seen in the present series with radiological sacroiliitis and ulcerative colitis and none with this radiological feature and Crohn's disease. This is probably a result of the method of patient selection, most patients being referred because of back symptoms, rather than being found by chance at a gastroenterological clinic as a result of examination of the sacroiliac joints on barium examination films.

A combined analysis has been performed (Table 5.6) using data from four other series. The combined relative risk (x) for HLA-B27 is 3.7 for which χ^2 (1 d.f) is 18.38 with $p = 1.8 \times 10^{-5}$. This suggests that there is an increased risk in patients with chronic inflammatory bowel disease of finding radiological sacroiliitis in HLA-B27 positive patients compared with those lacking this antigen. It should be noted, however, that the relative risk is significantly less than that for ankylosing spondylitis with chronic inflammatory bowel disease and HLA-B27. This suggests that pathologically and aetiologically asymptomatic radiological sacroiliitis is not synonymous with ankylosing spondylitis under these circumstances. Asymptomatic radiological sacroiliitis may represent two groups of patients, one predominantly HLA-B27 positive who will in future develop ankylosing spondylitis and the other predominantly HLA-B27 negative who will remain asymptomatic and not develop further progression. Against this is that the χ^2 for heterogeneity (7.63 with 4 d.f) between these five series is statistically small ($p > 0.1$). Only prolonged follow-up of patients found to have asymptomatic radiological sacroiliitis in association with chronic inflammatory bowel disease will determine if this radiological abnormality is a single entity or, in some patients, an early asymptomatic phase of a chronic symptomatic disorder (ankylosing spondylitis).

In the present series the frequency of HLA-B27 was higher, but not significantly higher, in those patients with uveitis (80%) compared with those who did not have

Table 5.6 Combined analysis of HLA-B27 frequencies in 5 series of caucasoids with chronic inflammatory bowel disease with radiological sacroiliitis alone

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Hyla, Frank and Davis (1976)	11	91	9.1	6.6	1.88	0.631	1.342	0.847	0.534
Mallas et al (1976)	17	283	41.2	6.7	9.69	2.271	3.708	8.421	19.124
Huaux et al (1977)	7	250	0.0	8.4	0.71	-0.340	1.175	-0.400	0.136
Dekker-Saeys et al (1978b)	15	778	26.7	9.9	3.54	1.265	3.360	4.251	5.377
Present series	2	451	0.0	8.2	2.18	0.781	1.362	1.064	0.831

$$Y = \sum wy / \sum w = 1.296 \text{ (95\% confidence limits = 0.704 and 1.888)}$$

$$x = \text{Antilog}_e Y = 3.65 \text{ (95\% confidence limits = 2.02 and 6.61)}$$

$$\chi^2 \text{ for significance of } Y = 18.38, \text{ for 1 d.f. } p = 1.8 \times 10^{-5}$$

$$\chi^2 \text{ for heterogeneity of } y's = 7.63, \text{ for 4 d.f. } p > 0.10$$

uveitis (37.5%). Similar higher frequencies of HLA-B27 have been found in patients with uveitis compared with those without by two other groups (Bluestone et al, 1975; Dekker-Saeyns et al, 1978). An analysis of the combined result (Table 5.7) shows that this increased frequency of HLA-B27 in patients with uveitis in association with ankylosing spondylitis and inflammatory bowel disease is significantly higher ($p = 2.3 \times 10^{-3}$) compared with similar patients who do not have uveitis. Statistical analysis does not suggest any heterogeneity between the three studies ($p \sim 1.0$).

HLA-B27 was more frequent in those patients where back symptoms preceded their bowel symptoms than in those whose back symptoms succeeded their bowel symptoms ($0.10 > p > 0.50$). Dekker-Saeyns et al (1978b) however, found a similar frequency of HLA-B27 in both such groups of patients they studied. Since the relative risk for ankylosing spondylitis in patients with chronic inflammatory bowel disease is significantly less than the relative risk for ankylosing spondylitis in persons not having chronic inflammatory bowel disease (Tables 5.1 and 5.3) analysis of a larger series of patients with regard to chronology of onset of the two diseases with regard to the presence or absence of HLA-B27 would be of some interest. It is possible that the presence of bowel disease could lead to the development of spinal disease in an HLA-B27 negative individual, whereas HLA-B27 would be necessary for the prior development of ankylosing spondylitis. Pelvic infection spreading via lymphatics

Table 5.7 Combined analysis of HLA-B27 frequencies in 3 series of caucasoids in patients with chronic inflammatory bowel disease and ankylosing spondylitis comparing patients with and without acute anterior uveitis.

Series	Number of patients with uveitis	Number of patients without uveitis	Percent of patients with uveitis HLA-B27 positive	Percent of patients without uveitis HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Bluestone et al (1975)	6	6	83.3	50.0	5.00	1.609	0.536	0.862	1.388
Dekker-Saeys et al (1978)	11	27	81.8	40.7	6.55	1.874	1.308	2.458	4.618
Present series	5	8	80.0	37.5	6.67	1.898	0.561	1.065	2.021

$Y = \sum wy / \sum w = 1.823$ (95% confidence limits = 1.178 and 2.468)
 $x = \text{Antilog}_e Y = 6.09$ (95% confidence limits = 3.25 and 11.80)
 χ^2 for significance of Y = 7.995, for 1 d.f. $p = 2.3 \times 10^{-3}$
 χ^2 for heterogeneity of y's = $\sum wy^2 - Y^2 \cdot \sum w = 0.032$, for 2 d.f. $p \sim 1.0$

and vertebral venous plexus has been suggested previously (Romanus, 1953) and it is possible that such a mechanism could be operating in HLA-B27 negative patients with ankylosing spondylitis and chronic inflammatory bowel disease whose spinal disease succeeds the onset of their bowel disease. Genetic factors may however also be implicated and not require the presence of bowel disease to predispose to the development of ankylosing spondylitis. This will be discussed further in the discussion of family data from the whole study (Section 6).

5.3 PSORIATIC ARTHRITIS

5.3.1 Clinical Features

Moll and Wright (1973b) have defined psoriatic arthritis as an inflammatory arthritis in a patient with psoriasis and a negative sensitized sheep cell test for rheumatoid factor. More recently Lambert and Wright (1977) have described a spondylitis with syndesmophytes but without sacroiliitis. Of the 79 patients in the present series only two females with seropositive rheumatoid arthritis do not satisfy these criteria. The results of several large series have shown that involvement of the distal interphalangeal joints of the fingers is characteristic of psoriatic arthritis (Wright, 1956; Baker, Golding and Thompson, 1964; Moll and Wright, 1973b) but the frequency of this type of involvement is variable. Moll and Wright (1973b) found only 5% of patients to have predominant involvement of these joints whereas Wright (1956) had found 26% and Baker, Golding and

Thompson (1964) had found 32% of their patients to have such involvement. The 54.4% prevalence of involvement of these joints seen in the present series is the same as the 54% found by Coste and Solnica (1966). Such variability in the clinical picture seen in psoriatic arthritis could easily arise from apparently minor differences in definition or the method of ascertainment, as well as possible geographical differences. The inclusion of all patients with distal interphalangeal joint involvement as in the present series will result in a higher prevalence of this type of arthritis than when this term is restricted to those patients with predominantly distal interphalangeal joint involvement. The pattern of joint involvement seen by the Leeds group (Moll and Wright, 1973b) is that of the rheumatologist in an established centre where a special interest has developed. The present series was largely referred by dermatologists for the purpose of the study and although all patients referred were seen it is possible that our colleagues did not refer all patients with relatively mild oligoarticular inflammatory disease. Hence, the patients in the present series may not represent a complete cross-section of the population of the area with psoriatic arthritis. For these reasons the results have been analysed for each group separately as well as for the combined series. It is interesting nevertheless to note that although the relative frequencies of the individual types of arthritis differ from those of Moll and Wright (1973b) examples of each type they recognise

were also seen in the present study.

The association between radiological sacroiliitis (Avilla et al, 1960; Dixon and Lience, 1961; Wright, 1961; Jajic, 1968) and ankylosing spondylitis (Wright, 1956) with psoriatic arthritis is well established. Therefore, in the analysis patients with and without such abnormalities have been analysed separately.

The almost equal sex incidence found in the present series is similar to that found by Coste and Solnica (1966) and Moll and Wright (1973b) who have noted that this differs from the female predominance of rheumatoid arthritis. Males predominated in the group with spinal disease and females in the group with joint involvement indistinguishable clinically or radiologically from seronegative rheumatoid arthritis. This male predominance in patients with radiological sacroiliitis is similar but not as marked as that found in the series of 119 patients with ankylosing spondylitis without psoriasis (χ^2 c = 8.02; $p = 2.3 \times 10^{-3}$).

Previous studies have found a high frequency of nail involvement in psoriatic arthritis (Wright, 1956; Baker, Golding and Thompson, 1964; Coste and Solnica, 1966; Moll and Wright, 1973b). The finding of nail abnormalities in 76.4% of patients is in accord with these other studies. In the present series nail involvement was found to be particularly associated with distal interphalangeal joint involvement. It is interesting to note that Baker, Golding and Thompson (1964) found

nail involvement to be associated with radiological involvement of the corresponding distal interphalangeal joint. In their series, however, this form of joint involvement did not have an overall higher frequency of nail involvement than in the other patients studied.

In the present series 7.6% of patients gave a history of acute anterior uveitis which is very similar to the 7.1% prevalence found by Lambert and Wright (1976). This form of eye involvement was particularly associated with ankylosing spondylitis (though not statistically significant) as found by these other workers.

5.3.2 Histocompatibility Testing

In the present series all eight patients with psoriasis and ankylosing spondylitis without peripheral arthritis were HLA-B27 positive. A high frequency of HLA-B27 in similar patients in three other series has been found (Table 5.8). The frequency of HLA-B27 in all four series is similar to that found in ankylosing spondylitis without psoriasis and the combined relative risk (x) of 55.27 is not significantly different from the 66.82 obtained for ankylosing spondylitis alone (Table 5.1).

In their original study Brewerton et al (1974) found a significantly increased frequency of HLA-B27 in patients with psoriatic peripheral arthritis alone. Some studies have confirmed this finding (Metzger et al, 1975; Karvonen, 1975) whereas others have found a similar frequency in patients as controls (Lambert et al,

Table 5.8 Combined analysis of HLA-B27 frequencies in 4 series of caucasoids with psoriasis and ankylosing spondylitis alone

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1974)	10	300	90.0	7.3	78.39	4.362	1.545	6.741	29.405
Lambert et al (1976)	7	1000	71.4	7.5	26.97	3.295	1.945	6.408	21.113
Espinoza et al (1978)	6	160	83.3	8.8	37.05	3.612	1.351	4.880	17.627
Present series	8	451	100.0	8.2	187.91	5.236	1.139	5.964	31.249

$Y = \sum wy / \sum w = 4.012$ (95% confidence limits = 3.210 and 4.814)
 $x = \text{Antilog}_e Y = 55.27$ (95% confidence limits = 24.78 and 123.22)
 χ^2 for significance of $Y = Y^2 \cdot \sum w = 96.27$, for 1 d.f. $p = 1.0 \times 10^{-22}$
 χ^2 for heterogeneity of y 's = $\sum wy^2 - Y^2 \cdot \sum w = 3.129$, for 3 d.f. $p > 0.30$

1976; Feldmann et al, 1976; Roux et al, 1977; Espinoza et al, 1978). The results of the present series also found a significantly increased frequency of HLA-B27 in patients with peripheral psoriatic arthritis ($p = 1.1 \times 10^{-3}$). A combined analysis (Table 5.9) of these eight series gives an overall relative risk (x) for HLA-B27 of 2.10 for which $Y^2 \sum w$ is 19.47 (1 d.f) and $p = 1.0 \times 10^{-5}$. This confirms that there is a significant association between peripheral psoriatic arthritis and HLA-B27. There is, however, heterogeneity between the individual estimates of y ($\chi^2 = 17.477$ (7 d.f); $p < 0.02$) confirming the marked differences in the frequencies of HLA-B27 in the individual series. Moll and Wright (1973b) have suggested criteria for the diagnosis of psoriatic arthritis and whilst some workers specifically used these criteria (Brewerton et al, 1974; Metzger et al, 1975; Espinoza et al, 1978) others have included all patients with inflammatory arthritis and psoriasis. In some only seronegative patients were included (Karvonen, 1975). Roux et al (1977) do not specifically state their criteria, but in an earlier report on a similar group of patients from the same centre (Sany et al, 1975) seropositive patients were included. It is possible, therefore, that differences in the frequency of HLA-B27 in patients with psoriasis and peripheral arthritis alone could occur because of differences in diagnostic criteria. All patients with peripheral arthritis in the present series, apart from two with seropositive rheumatoid arthritis who have been

Table 5.9 Combined analysis of HLA-B27 frequencies in 8 series of caucasoids with peripheral psoriatic arthritis alone

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1974)	41	300	24.4	7.3	4.13	1.417	5.909	8.374	11.865
Metzger et al (1975)	17	254	17.6	5.9	3.73	1.316	2.609	3.433	4.518
Karvonen (1975)	41	326	26.8	14.1	2.27	0.322	7.121	5.854	4.812
Lambert et al (1976)	54	1000	9.3	7.5	1.36	0.309	4.977	1.538	0.475
Feldmann et al (1976)	44	152	6.8	3.9	1.90	0.642	2.361	1.516	0.973
Roux et al (1977)	68	264	7.3	8.7	0.52	-0.651	4.384	-2.854	1.858
Espinoza et al (1978)	22	160	4.5	8.8	0.72	-0.325	1.616	-0.525	0.171
Present series	39	451	25.6	8.2	3.93	1.370	6.537	8.956	12.270

$Y = \sum wy / \sum w = 0.740$ (95% confidence limits = 0.411 and 1.069)
 $x = \text{Antilog } Y = 2.10$ (95% confidence limits = 1.51 and 2.91)
 χ^2 for significance of $Y = Y^2 \cdot \sum w = 19.47$, for 1 d.f. $p = 1.0 \times 10^{-5}$
 χ^2 for heterogeneity of y's = $\sum wy^2 - Y^2 \cdot \sum w = 17.48$, for 7 d.f. $p < 0.02$

excluded from the analysis, would satisfy the Moll and Wright (1973b) criteria for psoriatic arthritis. However, 54.4% of the total series in the present study were represented by patients with involvement of the distal interphalangeal joints in contrast to the 5% with this type found by Moll and Wright (1973b) (see Section 5.3.1). Unfortunately the numbers in each of the other groups of peripheral arthritis with peripheral arthritis alone are too small to make valid comparisons of the frequency of HLA-B27 in each of these groups. If this were to differ between the groups, though the present series do not lend any strong support for this, then it would be possible to have overall differences in the frequency of HLA-B27 between individual series depending upon the proportion of patients with each type of peripheral arthritis in these series. Analysis of large series of patients with peripheral psoriatic arthritis alone would be necessary to determine if such an influence was present.

The presence of radiological sacroiliitis or ankylosing spondylitis in addition to peripheral psoriatic arthritis in the present series is associated with a higher frequency of HLA-B27 (54.5%) than when peripheral psoriatic arthritis alone is present (25.6%). Similar results have been found in previous series (Metzger et al, 1975; Lambert et al, 1976) but Roux et al (1977) did not find any difference in frequency of HLA-B27 between such patients. A combined analysis of the present series together with four other published series (Table 5.10

Table 5.10 Combined analysis of HLA-B27 frequencies in 5 series of caucasoids with peripheral psoriatic arthritis and radiological sacroiliitis or ankylosing spondylitis.

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Metzger et al (1975)	23	254	34.8	5.9	8.47	2.137	4.162	8.894	19.006
Marcusson, Moller and Thyresson (1975)	11	100	63.6	14.0	9.94	2.297	2.480	5.697	13.087
Lambert et al (1976)	17	1000	76.5	7.5	36.78	3.605	3.501	12.620	45.494
Roux et al (1977)	22	264	9.1	8.7	1.25	0.225	2.343	0.527	0.119
Present series	22	451	54.5	8.2	13.16	2.577	5.088	13.111	33.786

$Y = \sum wy / \sum w = 2.324$ (95% confidence limits = 1.856 and 2.792)
 $x = \text{Antilog}_e Y = 10.22$ (95% confidence limits = 6.40 and 16.31)
 χ^2 for significance of $Y = Y^2 \cdot \sum w = 94.95$, for 1 d.f. $p = 2.0 \times 10^{-22}$
 χ^2 for heterogeneity of y 's = $\sum wy^2 - Y^2 \cdot \sum w = 16.54$, for 4 d.f. $p < 0.01$

gives an overall relative risk (x) for HLA-B27 in patients with peripheral arthritis and radiological sacroiliitis or ankylosing spondylitis of 10.22 which is significantly higher than that obtained for a similar analysis of eight series of patients with peripheral arthritis alone (Table 5.9). This suggests that psoriatic patients who are HLA-B27 positive have an increased risk of development peripheral psoriatic arthritis and a still higher risk of developing radiological sacroiliitis or ankylosing spondylitis compared with psoriatic patients who do not have this antigen.

The frequency of HLA-B27 in all patients with ankylosing spondylitis or radiological sacroiliitis and psoriasis in the present series is significantly higher than controls ($p = 1.4 \times 10^{-20}$). In addition a significantly lower frequency of this antigen in these patients has been found than in patients without peripheral arthritis ($p = 0.018$) and patients with ankylosing spondylitis without psoriasis ($p = 6.7 \times 10^{-4}$). Frequencies of HLA-B27 similar to that in the present series in this type of patient have been found in three other series (Table 5.11). A combined analysis gives an overall relative risk (x) of 21.20 which is lower, but not significantly, than the value of 55.27 for patients with ankylosing spondylitis with psoriasis but without peripheral arthritis (Table 5.8). It is significantly lower than the value of 66.82 for patients with ankylosing spondylitis without psoriasis (Table 5.1).

Table 5.11 Combined analysis of HLA-B27 frequencies in 4 series of caucasoids with psoriasis and ankylosing spondylitis with and without peripheral psoriatic arthritis.

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Lambert et al (1976)	24	1000	75.0	7.5	36.78	3.606	4.768	17.194	62.001
Feldmann et al (1976)	26	152	50.0	3.9	22.54	3.115	3.419	10.649	33.171
Roux et al (1977)	18	264	50.0	8.7	10.28	2.330	4.068	9.479	22.087
Present series	30	451	66.7	8.2	21.58	3.072	5.979	18.367	56.424

$Y = \sum wy / \sum w = 3.054$ (95% confidence limits = 2.595 and 3.513)
 $x = \text{Antilog}_e Y = 21.20$ (95% confidence limits = 13.40 and 33.55)
 χ^2 for significance of $Y = Y^2 \cdot \sum w = 170.08$, for 1 d.f. $p = 7.4 \times 10^{-39}$
 χ^2 for heterogeneity of y's = $\sum wy^2 - Y^2 \cdot \sum w = 3.60$, for 3 d.f. $p > 0.20$

This suggests that a patient with psoriasis but who is HLA-B27 negative has a higher risk of developing ankylosing spondylitis with a peripheral arthritis than a similar person without psoriasis has of developing ankylosing spondylitis. This will be discussed further when considering ankylosing spondylitis in HLA-B27 negative subjects (Section 6.3.2).

No increase in the frequency of HLA-B13 was found in the present series. This antigen has been found in increased frequency in psoriatic patients (Russell et al, 1972; White et al, 1972; Seignalet et al, 1974; Schunter and Schieferstein, 1974) but Woodrow et al (1975) found only a slight increase in frequency of this antigen in 157 patients with psoriasis (7.2%) in Liverpool compared with 233 controls (5.2%). They comment that there appears to be a reciprocal relationship between the frequency of HLA-B13 and HLA-BW17 in psoriatic patients from different populations. The lack of an increase in the frequency of HLA-B13 in the present series of patients with psoriatic arthritis suggests that this antigen is associated with psoriasis rather than its associated arthritis. No other report of an increase in this antigen in patients with psoriatic arthritis has been noted when the association between HLA-B13 and psoriasis in the same population is not marked.

In contrast HLA-BW17 was found with an increased frequency in the present series. It is noteworthy that it was this antigen which Woodrow et al (1975) found to be present in a high frequency (48.4%) in patients with

psoriasis in Liverpool compared with controls (6.0%). They found a high frequency of a positive family history of psoriasis in HLA-BW17 positive patients with psoriasis but this was not found in the present series. Previous workers have commented on the reciprocal relationship between the frequency of HLA-BW17 and HLA-B27 in patients with psoriatic arthritis, HLA-B27 being especially associated with radiological sacroiliitis and ankylosing spondylitis and HLA-BW17 with peripheral arthritis and more so with psoriasis without arthritis (Metzger et al, 1975; Feldmann et al, 1976; Roux et al, 1977). The results of the present series would lend support to this view.

Histocompatibility antigens, however, are allelic, an increased frequency of one in a population leading to a decreased frequency of the others determined at the same genetic locus. Being HLA-BW17 is an important risk factor for the development of psoriasis in Liverpool (Woodrow et al, 1975). Having psoriasis and being HLA-B27 positive is an important risk factor in the same population for the development of an arthropathy, both peripheral and sacroiliac, but particularly sacroiliac. The presence of HLA-BW17 in an individual does not preclude the development of arthropathy, but the decreasing frequency of HLA-BW17 with the increasing frequency of HLA-B27 in the psoriatic population depending upon the presence and type of arthropathy and the absence of an increased frequency of HLA-B27 in psoriatic patients without arthritis suggests that being HLA-B27 is an

important genetic factor for the development of arthritis, whereas being HLA-BW17 is an important genetic factor for the development of the skin lesion.

5.4 REITER'S SYNDROME

5.4.1 Clinical Features

It has been suggested that the term Reiter's syndrome should be reserved to describe those patients presenting with the triad of urethritis, conjunctivitis and arthritis and to use Reiter's disease as a diagnostic term for patients who have an arthritis with urethritis but lacking the full triad of symptoms (Wright and Moll, 1976). Such a distinction, however, has not been made by previous workers, the two terms having been used synonymously (Corner, 1950; Montgomery et al, 1956; Csonka, 1958; Csonka, 1959; Mesbernard, 1959; Jacobs, 1961; Grimble, 1963; Lockie and Hunder, 1971; Woodrow, Treanor and Usher, 1974; Morris et al, 1974a; McClusky, Lordon and Arnett, 1974; McGlamory, 1976; Good and Schultz, 1977; McCord, Nies and Louie, 1977). In the present study the term Reiter's syndrome has been used to include all patients with an arthritis occurring in association with urethritis or other urogenital manifestations normally seen in patients with the full triad.

The various clinical features seen in patients in the present study were present with similar frequencies to those found in previous large series. The 68.8% incidence of conjunctivitis in the present series is in

accord with the 67% incidence reported by McCord, Nies and Louie (1977) though higher than the lower incidence of 32% reported by Csonka (1958). Another recent study where the presence of conjunctivitis has been specifically recorded found an incidence of 50% (Zachariae et al, 1975). The low incidence reported by Csonka could be due to his study being entirely retrospective, whereas in the present series and other recent series the patients were studied either prospectively or reviewed at the time of the study.

Acute anterior uveitis has been found equally frequently in those series where it has been reported. Csonka (1958) reported a 10.8% incidence, Zachariae et al (1975) 10.4% and in the present series 13.0% of patients had acute anterior uveitis at some time.

Balanitis was found in a high proportion (78.9%) of the 38 patients reported by Montgomery et al (1956) whereas Csonka (1958) found only 20.5% of his large series to be affected. More recent studies (McClusky, Lordon and Arnett, 1974; Zachariae et al, 1975) have reported an incidence of between a third and half their patients affected. The 32.5% incidence seen in the present series is similar to these more recent studies. It is difficult to know why balanitis was found so frequently by Montgomery et al (1956) compared with subsequent workers, but it is of interest to note the rather high frequency (28.9%) of keratoderma blenorrhagica found by them and the association they

found between the presence of balanitis and keratoderma blenorrhagica. This, however, is not an entirely satisfactory explanation as McClusky, Lordon and Arnett (1974) found an even higher incidence of keratoderma blenorrhagica (40%) but only a 47% incidence of balanitis. Selection of patients and the zeal of the observer may be a factor in the differing frequency of reporting of these clinical features.

A high incidence of keratoderma blenorrhagica has been found in some studies (Montgomery et al, 1956; McClusky, Lordon and Arnett, 1974) but others (Csonka, 1958; Zachariae et al, 1975) have found an incidence similar to the 15.6% in the present series.

One patient without urethritis has been included in the small personal series of 22 patients. He had other clinical features to suggest the diagnosis of Reiter's syndrome. Similarly Csonka (1958) included 16 (8.6%) patients in his large review of Reiter's syndrome who did not have urethritis. In all other respects they were similar to the other patients in his series.

5.4.2 Histocompatibility Testing

The high frequency of HLA-B27 in patients with Reiter's syndrome compared with controls is confirmed in the present study. A combined analysis of the present series and three others with more than 40 patients together with the two original reported series (Brewerton et al, 1973b; Morris et al, 1974a) is shown in Table 5.12. The combined relative risk (x) for

Table 5.12 Combined analysis of HLA-B27 frequencies in 6 series of caucasoids with Reiter's syndrome.

Series	Number of patients	Number of controls	Percent of patients HLA-B27 positive	Percent of controls HLA-B27 positive	Relative risk x	y = ln.x	w	wy	wy ²
Brewerton et al (1973)	33	33	75.8	6.1	37.80	3.632	1.945	7.064	25.656
Morris et al (1974a)	24	1863	95.8	8.1	177.09	5.177	1.822	9.433	48.834
Aho et al (1974)	40	326	90.0	14.1	48.83	3.890	3.970	15.445	60.081
Amor et al (1974)	46	152	80.4	4.0	88.97	4.488	3.624	16.262	72.985
Zachariae et al (1975)	48	2103	64.6	8.1	20.41	3.016	10.733	32.371	97.630
Present series	77	451	71.4	8.2	27.27	3.306	11.104	36.709	121.358

$$Y = \sum wy / \sum w = 3.533 \text{ (95\% confidence limits = 3.193 and 3.873)}$$

$$x = \text{Antilog}_e Y = 34.22 \text{ (95\% confidence limits = 24.36 and 48.09)}$$

$$\chi^2 \text{ for significance of } Y = Y^2 \cdot \sum w = 414.35, \text{ for 1 d.f. } p = 4.5 \times 10^{-92}$$

$$\chi^2 \text{ for heterogeneity of } y's = \sum wy^2 - Y^2 \cdot \sum w = 12.20, \text{ for 6 d.f. } p < 0.05$$

HLA-B27 is 34.22 for which $Y^2 \cdot \sum w$ is 414.35 (1 d.f) and $p = 4.5 \times 10^{-92}$. There is, however, some evidence of heterogeneity between the individual relative risks ($p < 0.05$) and examination of these shows a very high value of 178 obtained by the Los Angeles group (Morris et al, 1974a) compared with values less than half this in the remaining four series. It is noteworthy that Morris et al (1974a) found radiological sacroiliitis in 25% of their patients compared with only 16.7% and 13.0% in the patients studied by Zachariae et al (1975) and in the present series respectively. Although not statistically significant, possibly owing to the small numbers in each series, the general experience, both in the present series and others (Brewerton et al, 1973b; Morris et al, 1974a; Zachariae, 1975) is that most patients with radiological sacroiliitis are HLA-B27 positive. An excess of patients with radiological sacroiliitis when compared with those of other series could be an explanation of the high relative risk found by Morris et al (1974a). In support of this a combined analysis of the other five series alone gives only a slightly reduced overall relative risk (x) of 31.19 but without statistical evidence of significant heterogeneity ($\chi^2 = 6.94$ (4 d.f); $p > 0.10$).

The presence or absence of conjunctivitis does not appear to be influenced by the presence or absence of HLA-B27. Almost identical frequencies for HLA-B27 were found for patients with conjunctivitis (73.6%) and the whole series (71.4%) in the present study. This finding

would support the view that the separation by terminology of patients with the classical triad of symptoms from those lacking a feature is probably artificial and unnecessary.

Other clinical features, however, may be influenced by the presence or absence of HLA-B27. In the present series uveitis particularly occurred in HLA-B27 positive patients. The results of studies by Brewerton et al (1973b), McClusky, Lordon and Arnett (1974) and Zachariae et al (1975) were similar. In addition keratoderma blenorrhagica was found in the present series to be more frequent in HLA-B27 positive patients.

It appears, therefore, that being HLA-B27 positive has no influence on the presence of the classical triad of symptoms in complete or incomplete form, but may influence the development of the less common features, particularly acute anterior uveitis, keratoderma blenorrhagica and radiological sacroiliitis.

In view of the genetic association between Reiter's syndrome and psoriasis (Lawrence, 1974) it is of interest to note the lack of any significant increase in frequency of HLA-B13 or HLA-BW17 in the present series of patients with Reiter's syndrome. Identical findings have been reported by others (Brewerton et al, 1973b; Morris et al, 1974a; Zachariae et al, 1975). This does not exclude an influence of those HLA types on the development of Reiter's syndrome, since, as has been argued elsewhere (Section 5.3.2) an increased frequency of one

histocompatibility antigen inevitably will result in a reduced frequency of the others. In addition the presence of HLA-B13 and HLA-BW17 are probably not the only genetic factors predisposing to psoriasis (Woodrow et al, 1975), hence other unknown genetic factors predisposing to psoriasis could influence the development of Reiter's syndrome.

5.5 ACUTE ANTERIOR UVEITIS

5.5.1 Clinical Features

The present series of 90 patients with acute non-granulomatous uveitis has been reported in detail elsewhere (Mapstone and Woodrow, 1975). The purpose of the present review was to define more certainly the associated disorders in individual patients. The larger proportion of patients with ankylosing spondylitis in the present review (17.8%) than in the original report (11.1%) is due to the diagnosis of definite ankylosing spondylitis in patients not previously fully examined and the change in diagnosis from osteitis condensans ilii to ankylosing spondylitis in two females. These changes in diagnosis were made without knowledge of the histocompatibility antigens of each patient. This frequency of ankylosing spondylitis is similar to that found by Catterall (1960) in a large group of patients from a hospital uveitis clinic. Catterall (1960) however found more Reiter's syndrome (23%) than in the present series (3.9%) in males. The reason for this difference is not apparent though it should be noted that

he was looking for evidence of chronic prostatitis and this raises the possibility of a bias towards seeing and obtaining the co-operation of patients with a disease with urogenital symptoms. The lower prevalence of Reiter's syndrome in the present series is similar to the 6% prevalence found by Brewerton (1975) in a similar study.

5.5.2 Histocompatibility Testing

The high frequency of HLA-B27 found by Brewerton (1975) in a hospital group of patients with acute non-granulomatous uveitis is confirmed. Other studies (Russell et al, 1976; Saraux et al, 1976) have also found an overall frequency of approximately 60%. These three studies have also noted the especially high frequency of HLA-B27 in those patients also found to have ankylosing spondylitis. In addition the present series and Brewerton (1975) found an association between Reiter's syndrome and radiological sacroiliitis and HLA-B27 in patients with acute anterior uveitis. If patients with associated diseases are excluded the frequency of HLA-B27 in patients with acute anterior uveitis remains significantly increased ($p = 6 \times 10^{-12}$). The overall frequency of 45.2% for HLA-B27 in such patients in the present series is similar to the frequency of 43.8% and 36.6% found by Brewerton (1975) and Saraux et al (1976) respectively. These other series have also found an equal sex distribution of HLA-B27 in such patients.

The association between acute anterior uveitis and HLA-B27 with an especial association in those patients with ankylosing spondylitis suggests that being HLA-B27 positive predisposes to the development of both. The association between HLA-B27 and ankylosing spondylitis alone suggests that although being HLA-B27 positive may predispose to both ankylosing spondylitis and acute anterior uveitis, that other factors may determine the clinical manifestations of disease in any one individual.

In addition to an especial association of ankylosing spondylitis and HLA-B27 in patients with acute anterior uveitis both the present series and others (Brewerton, 1975; Saraux et al, 1976) have found a male predominance in such patients compared with equal sex incidence in both HLA-B27 positive and negative patients in those without associated disease. This is further evidence in support of independence of development of ankylosing spondylitis and acute anterior uveitis since one would expect a male predominance in patients with acute anterior uveitis, similar to that in ankylosing spondylitis if the predisposing features were identical for the two diseases.

CHAPTER 6

GENETIC IMPLICATIONS OF THE

ASSOCIATION OF HLA-B27

AND THE SERONEGATIVE SPONDARTHRTIDES

Having established that the seronegative spondarthritides (Wright and Moll, 1976) are associated with the antigen HLA-B27 determined by an allele at the B locus of the major histocompatibility complex we need to consider whether we have any information as to how this association has occurred and what other factors, if any, are necessary for the development of clinical disease. The available data will be discussed under these main headings:

1. the prevalence of ankylosing spondylitis in HLA-B27 positive individuals
2. the possible role of environmental factors
3. the prevalence of disease in HLA-B27 positive individuals
4. the role of genes for psoriasis and chronic inflammatory bowel disease in ankylosing spondylitis
5. families with multiple examples of seronegative spondarthritides.

6.1 THE PREVALENCE OF ANKYLOSING SPONDYLITIS IN
HLA-B27 POSITIVE INDIVIDUALS

6.1.1 Ankylosing spondylitis in Caucasians

In their postal survey of 2400 blood donors Calin and Fries (1975) found approximately 20% of HLA-B27 positive donors, both male and female, to have definite ankylosing spondylitis according to the New York Criteria (Bennett and Wood, 1968). In a more detailed clinical and radiological follow-up of donors who had not had previous radiographs to include the sacroiliac joints a further two HLA-B27 positive blood donors were found with ankylosing spondylitis (Calin et al, 1977a). In addition two HLA-B27 negative blood donors previously diagnosed as having "mechanical backache" were found to have ankylosing spondylitis. The addition of these two HLA-B27 positive blood donors to the six of 30 HLA-B27 positive blood donors with ankylosing spondylitis found in their earlier study would raise the prevalence of this disease in male HLA-B27 blood donors to 26.7%.

A similar postal survey of 2000 male blood donors has been performed by Cohen et al (1976). They found 12.5% of HLA-B27 males to have definite ankylosing spondylitis satisfying the New York Criteria (Bennett and Wood, 1968) and the same proportion with radiological sacroiliitis. In addition to reading radiographs for erosion, sclerosis, alteration in joint width and ankylosis they also noted the presence or absence of "cortical breaks". From an illustrated example of these

many would consider these as small erosions. If these "cortical breaks" had been read as erosions then an additional two HLA-B27 positive males would have been diagnosed as having ankylosing spondylitis according to the New York Criteria (Bennett and Wood, 1968) giving an overall prevalence of 20.8% for this disease in HLA-B27 positive male blood donors.

In Sardinia, Contu, Capelli and Sale (1977) have prospectively examined, clinically and radiologically, 26 HLA-B27 positive blood donors for evidence of ankylosing spondylitis and found the disease in 18.1% and 13.3% of males and females respectively compared with no evidence of the disease in 50 HLA-B27 negative individuals.

These recent estimates should be compared with those obtained from earlier population studies. The most satisfactory of these were the Leigh and Wensleydale surveys which gave a combined prevalence of ankylosing spondylitis of 0.4% in males (Lawrence, 1963). The calculated prevalence of 0.05% derived by West (1949) is unsatisfactory as this was based on a hospital population who had received radiotherapy. The controls used by de Blécourt, Polman and de Blécourt-Meindersma (1961) whilst ideal for the family study performed are not suitable for an estimate of the population prevalence of ankylosing spondylitis as selective factors were operating to reduce the possibility of finding this disease in controls.

Assuming a population frequency of HLA-B27 of 8% in the British population (present series) and the prevalence of ankylosing spondylitis in 0.4% of males in that population as found by Lawrence (1963) and assuming that all affected individuals are HLA-B27 positive would give a prevalence of this disease in HLA-B27 males of 5%. This is considerably lower than the 18 - 27% found by Calin and Fries (1975), Cohen et al (1976) and Contu, Capelli and Sale (1977). It is possible to argue that these latter estimates are artificially high being derived from a selected population. In this regard it is noteworthy that Calin and Fries (1975) and Contu, Capelli and Sale (1977) found an almost equal prevalence of the disease in males and females. This is contrary to the findings in large reported series of patients with ankylosing spondylitis (Hart and MacClagan, 1955; Wilkinson and Bywaters, 1958), though Parr, White and Shipton (1951) found an equal sex incidence. In addition in their first report Calin and Fries (1975) used radiographs already available, i.e. all patients should have been previously diagnosed. Selective factors may have been operating in their ascertainment by studying blood donors. Despite such reservations the similarity of the results of these three recent studies (Calin and Fries, 1975; Cohen et al, 1976; Contu, Capelli and Sale, 1977) is striking.

Examination of the data from which the British population prevalence of ankylosing spondylitis of 0.4% of males is derived (Lawrence, 1963) shows that in the

second Leigh survey (Kellgren and Lawrence, 1956) two males were found with ankylosing spondylitis out of 173 males with radiographs of the pelvis. Assuming that ankylosing spondylitis was only diagnosed in the presence of radiologically abnormal sacroiliac joints this gives a population prevalence of this disease of 1.2%.

Using a similar computation as above this gives an estimated prevalence of ankylosing spondylitis in HLA-B27 positive males of 15%, which is of a similar order to that found by Calin and Fries (1975), Cohen et al (1976) and Contu, Capelli and Sale (1977). The Wensleydale survey (Bremner, 1961) yielded three males with ankylosing spondylitis in a total male population of 870 giving a prevalence of this disease of 0.3% of males. It is the combination of this low prevalence with that obtained from the Leigh survey (Kellgren and Lawrence, 1956) which results in the combined prevalence of 0.4% (Lawrence, 1963). In the Wensleydale survey (Bremner, 1961) only selected individuals were x-rayed on the basis of symptoms, 175 males over the age of 55 years having pelvic radiographs. Assuming that ankylosing spondylitis was only diagnosed in the presence of radiologically abnormal sacroiliac joints then a prevalence of this disease in 1.7% of x-rayed males is obtained. Assuming a population frequency of HLA-B27 of 8% in Britain (present series) and all three individuals with ankylosing spondylitis to be HLA-B27 positive the prevalence of this disease in HLA-B27 positive males can be calculated to be 21.3%. Combining

these calculated prevalences for ankylosing spondylitis in males from the Leigh (Kellgren and Lawrence, 1956) and Wensleydale (Bremner, 1961) surveys gives an overall male population prevalence of 1.4%, and a prevalence in male HLA-B27 positive individuals of 17.5%.

Whilst assumptions, which may not be valid, have been made concerning the methodology of the Leigh (Kellgren and Lawrence, 1956) and Wensleydale (Bremner, 1961) surveys in the above revision of the estimated prevalence of ankylosing spondylitis obtained from these surveys it is important to note that these surveys were primarily concerned with determining the prevalence of the more common inflammatory and degenerative rheumatic diseases (Bremner, 1977). This is in contrast to the specific study of ankylosing spondylitis undertaken in more recent studies (Calin and Fries, 1975; Cohen et al, 1976; Contu, Capelli and Sale, 1977). It is noteworthy that the revised estimate for the prevalence of ankylosing spondylitis of 1.4% obtained from an analysis of the Leigh (Kellgren and Lawrence, 1956) and Wensleydale (Bremner, 1961) surveys resulting in an estimated prevalence of this disease in 17.5% of HLA-B27 males is similar to those more recent direct estimates (Calin and Fries, 1975; Cohen et al, 1976; Contu, Capelli and Sale, 1977).

However, no females were found with ankylosing spondylitis in the Leigh (Kellgren and Lawrence, 1956) and Wensleydale (Bremner, 1961) surveys in contrast to the equal prevalence in males and females found by

X
Calin and Fries (1975) and Contu, Capelli and Sale (1977). Calin and Fries (1975) have argued that the male sex predominance usually found in ankylosing spondylitis is due to a natural reluctance to irradiate female pelvises either diagnostically in symptomatic referred individuals or in population surveys. In the present series all 90 individuals presenting with acute anterior uveitis had an AP radiograph of the pelvis but only 25% of all 20 patients found with ankylosing spondylitis were female compared with 43.3% of the total series. Almost identical results were reported by Brewerton (1975) for his series of 100 patients with acute anterior uveitis. In addition no mothers were found with either radiological sacroiliitis or ankylosing spondylitis in the present detailed study of parents of ankylosing spondylitis probands. This lack of disease in mothers is in contrast to the 17.4% prevalence of ankylosing spondylitis found in the fathers. Emery and Lawrence (1967) were unable to find any mothers of ankylosing spondylitis probands compared with this disease in 16.7% of fathers studied. They did, however, find an almost equal sex prevalence in male (15.9%) and female (16.7%) siblings.

In summary it would appear that it is probable that the prevalence of disease in HLA-B27 positive male caucasians in the general population is of the order of 18 - 27% but the prevalence in a similar group of females is less certain.

6.1.2 Ankylosing spondylitis in other races

It is known that the frequency of HLA antigens including HLA-B27 varies in different populations (Histocompatibility Testing, 1972). Since this could affect the population prevalence of ankylosing spondylitis it is interesting to examine the available data (Table 6.1). It can be seen that as the frequency of HLA-B27 increases in the population so does the prevalence of ankylosing spondylitis. Unfortunately the prevalence data for ankylosing spondylitis in these five populations is of variable certainty. As can be seen from the above discussion on the prevalence of ankylosing spondylitis in Caucasians, which have been an extensively studied group, it is difficult to be certain that the overall prevalence of this disease in males is of the order of 1.5%. The Haida and Bella Coola North American Indians were studied prospectively and specifically for ankylosing spondylitis (Gofton et al, 1972). All studies of these two populations have found a high incidence of sacroiliac disease (Robinson, Gofton and Price, 1963; Gofton, Robinson and Trueman, 1966; Gofton et al, 1966). The prevalence of the disease in the North American Negro (Baum and Ziff, 1971) and Japanese (Tsujimoto, 1970) are both estimates rather than from the direct study of a random population sample.

Despite these reservations it is of interest to note that the correlation coefficient (r) for the frequency of HLA-B27 and prevalence of ankylosing

Table 6.1 Frequency of HLA-B27 and prevalence in males
of ankylosing spondylitis in five populations.

Population	Frequency of HLA-B27 %	Prevalence in males of ankylosing spondylitis %
Haida Indians	50.5 ¹	9.4 ²
Bella Coola Indians	25.6 ¹	5.2 ²
Caucasians	8.2 ³	1.5 ⁴⁻⁸
North American Negro	1.8 ⁹	0.5 ¹⁰
Japanese	2.3 ¹¹	0.03 ¹²

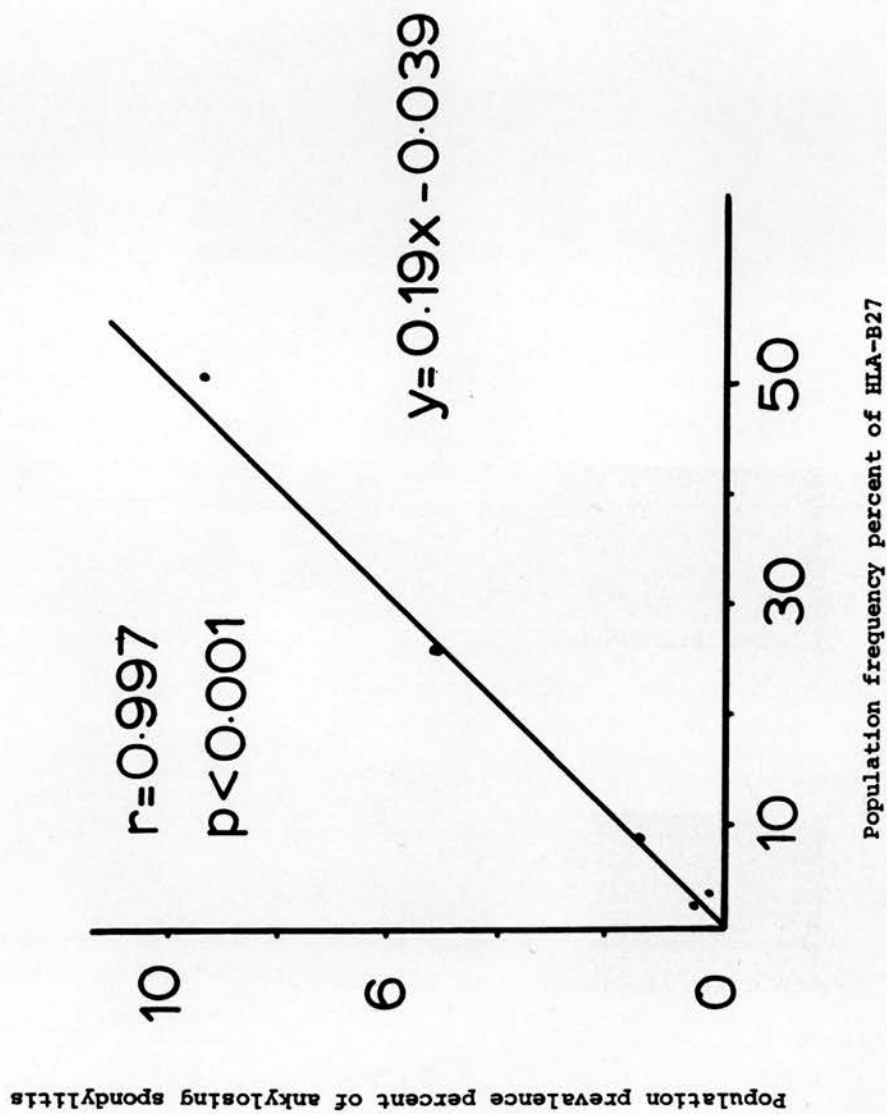
1. Gofton et al (1975)
2. Gofton et al (1972)
3. Present Series
4. Calin and Fries (1975)
5. Cohen et al (1976)
6. Contu, Capelli and Sale (1977)
7. Kellgren and Lawrence (1956)
8. Bremner (1961)
9. Payne et al (1977)
10. Baum and Ziff (1971)
11. Tsujimoto, Hichakawa and Shirakura (1975)
12. Tsujimoto (1970)

spondylitis in males for these five populations is 0.997 (Figure 6.1). Using the Fisher-Z transformation the p value for this estimate of r is <0.001 . By the method of least-squares the regression line is found to have the formula $y = 0.19.x - 0.039$ where y is the prevalence per cent of ankylosing spondylitis and x is the frequency per cent of HLA-B27 in a given population. This suggests that 19% of HLA-B27 positive males will develop ankylosing spondylitis irrespective of their race.

One racial group has been excluded from the above analysis. This is the Pima Indian of North America in whom two groups (Spees et al, 1973; Calin et al, 1977b) have found a frequency of HLA-B27 of 18%. The reason for exclusion is the marked uncertainty of the prevalence of ankylosing spondylitis and sacroiliitis. In three separate studies (Gofton et al, 1968; Gofton et al, 1972; Calin et al, 1977b) the prevalence in males of grades 2 - 4 radiological sacroiliitis was found to differ five-fold and grades 3 - 4 sacroiliitis ten-fold. This could be due to the presence of fluorosis which has a high prevalence in this population (Gofton et al, 1968) though subsequent workers (Calin et al, 1977b) found no difficulty in distinguishing the changes of sacroiliitis from those of fluorosis. It is difficult to suggest an alternative explanation for such marked differences in the prevalence of radiological sacroiliitis from the data available. In addition to differences in the prevalence of radiological sacroiliitis in males it must be noted that this has been found to be lower than

Figure 6.1 Regression line of population prevalence
percent of ankylosing spondylitis against
population frequency percent of HLA-B27
in five populations (Table 6.1)

fig. 6.1



in females (Calin et al, 1977b). In addition Calin et al (1977b) found an association between HLA-B27 and male Pima Indians but not in females. These two findings are so different from other populations which have been studied that caution should be advised in interpreting the available data on this population.

The constant -0.039 could represent the HLA-B27 negative individuals who develop ankylosing spondylitis. If this were so a positive value would have been expected. Allowing for the small number of populations used to derive this regression line it is possible that the true value of this constant (b) could have positive or a negative value. If it had a positive value then it would be expected that as the population frequency of HLA-B27, and hence the value of $0.19.x$, falls then the contribution to the total value of y by the constant (b) would increase, i.e. the proportion of HLA-B27 negative patients in any series of patients with ankylosing spondylitis derived from that population would increase. The North American Negro population is one in which several studies have been performed (Table 6.2). It can be seen that in four of these five studies a lower frequency of HLA-B27 was found in North American Negroes with ankylosing spondylitis than in North American whites. In one of these (Khan et al, 1977) this difference was found to be statistically significant at the 0.1% level.

In a study of a North African Arabian population where the population frequency of HLA-B27 was found to

Table 6.2 Frequencies of HLA-B27 in North American
Blacks and Whites with ankylosing spondylitis.

Series	Frequency of HLA-B27 in Blacks	Frequency of HLA-B27 in Whites
Swezey, Zucker and Terasaki (1974)	60.0	ND
Good, Kawanishi and Schultz (1976)	60.0	97.1
Levitia, Gough and Davis (1976)	81.0	82.0
Ruderman and Ward (1977)	53.8	100.0
Khan et al (1977)	48.0	94.0

be 5% compared with 7% in the French population Meunier, Maignan and Betwel (1977) found a lower frequency (61.5%) for HLA-B27 in the Arabian population compared with the French population (86.7%). Doury et al (1976) studied a similar population and with similar findings and concluded that the lower frequency for HLA-B27 found in army personnel with ankylosing spondylitis compared with a similar group of civilians was the result of differences in the hygiene of their quarters. In view of the findings in the North American Negro (Table 6.2) and in another North African Arabian population (Meunier, Maignan and Betwel, 1977) the alternative explanation that the difference in frequency of HLA-B27 in patients from the two groups is due to a racial effect must be considered.

In their study of the Israeli population Brautbar et al (1977) found frequencies for HLA-B27 in patients with ankylosing spondylitis and in controls of 79% and 3% respectively. These are both less than for a caucasian population.

In contrast Sengupta et al (1977) found a frequency for HLA-B27 of 94% in a Northern Indian population compared with only 3% in population controls from the same area. Tsujimoto, Hichikawa and Shirakura (1975) also found a frequency (91.7%) for HLA-B27 in Japanese patients similar to that found in caucasians whereas their controls had a much lower frequency (2.3%) of HLA-B27 than in a caucasian population.

In summary the evidence from different racial groups suggests that 19% of HLA-B27 positive males are likely to develop ankylosing spondylitis irrespective of race. In addition one would, in general, expect that as the population frequency of HLA-B27 falls then a greater proportion of patients with ankylosing spondylitis in that population will be HLA-B27 negative compared with a population with a high frequency of HLA-B27.

6.2 THE POSSIBLE ROLE OF ENVIRONMENTAL FACTORS

6.2.1 In Ankylosing Spondylitis

One possible explanation for only one fifth of all HLA-B27 males developing ankylosing spondylitis is that random environmental factors affecting approximately 20% of individuals could be necessary. Some evidence for the necessity of environmental factors comes from the study of monozygotic twins. In the present series two pairs of monozygotic twins were found in whom only one twin in each pair had ankylosing spondylitis (Pedigrees P.35 and P.36). The ages of these twins were 52 years and 45 years respectively. It could be argued that the second unaffected twin may develop the disease in the future. The overall results for age of onset of disease in the present study, however, are against such a possibility. Only 4.3% of patients first developed the disease after the age of 45 years. The third pair of identical twins (Pedigree P.10) aged 59 years are also of some interest. One of these (II₃) had severe clinical and radiological disease whereas his identical

twin brother (II_2) had no symptoms, normal spinal movements and bilateral grade 3 radiological sacroiliitis. It is possible to argue that this represents concordance for this disease, the one twin (II_2) having developed the disease more recently than the other (II_3). The clinically mild nature of disease in one twin (II_2) compared with his identical twin brother (II_3) and their age raises the possibility of the alternative explanation that different environmental factors have led to marked differences in the severity of their diseases. It is of interest to note that they are also discordant for acute anterior uveitis. Whilst this feature may first occur at any time in the course of ankylosing spondylitis discordance for this feature also suggests the possibility of environmental factors having a role in its development.

Moesmann (1960) found concordance for ankylosing spondylitis in one male pair and discordance in one female pair of identical twins. From the literature (Rogoff and Freyberg, 1948; Polley, 1948; Stephens and Nunemaker, 1950) he found a further five concordant pairs and a further two discordant pairs of identical twins. Subsequently only concordant identical twins have been reported (Kuthan and Navratil, 1966; Emery and Lawrence, 1967; Truong et al, 1975). Persistent discordance for ankylosing spondylitis in identical twins is strong evidence in favour of a role for environmental factors in the development of the disease. No sequential study of identical twins has been performed to determine the

relative importance of genetic and environmental factors.

Romanus (1953) found a high prevalence of genitourinary infection, particularly prostatic-vesiculitis in patients with ankylosing spondylitis. He suggested that the spinal disease resulted from the lymphatic spread of genitourinary infection to the spine. Although no controls were studied Mason et al (1958) in their study of chronic prostatitis found a significantly higher prevalence in patients with ankylosing spondylitis than in those with rheumatoid arthritis. No microorganisms, however, have ever been isolated from prostatic smears from such patients and Oates (1959) noted that giving tetracyclines did not improve the patients symptoms.

Recent interest has been further stimulated in the possible role of infection in the aetiology of ankylosing spondylitis by the findings of Ebringer et al (1977, 1978) of an association between faecal recovery of *Klebsiella pneumoniae* and active ankylosing spondylitis. These findings, however, have not yet been confirmed by other workers (Eastmond, Cooke and Wright, 1978; Brewerton and Warren, 1978).

6.2.2 In Reiter's syndrome and reactive arthritis

One type of arthritis in this genetically related group of diseases, the seronegative spondarthritides, where the role of environmental factors is more certain than in ankylosing spondylitis is in the reactive arthritides including Reiter's syndrome. In his

description of the disease Reiter (1916) considered the arthritis following acute dysentery to be due to syphilis. *Treponema pallidum* has not subsequently been found to have any aetiological role in the disease. Four apparent precipitants of these reactive arthritides have been described:

- i) *Salmonella typhimurium* (Berglof, 1963; Vartiainen and Hurri, 1964) and *Salmonella enteritidis* (Warren, 1970; Iveson et al, 1975).
- ii) *Shigella flexner* dysentery (Paronen, 1948; Corner, 1950; Masbernard, 1959; Noer, 1966; Locki and Hunder, 1971).
- iii) *Yersinia enterocolitica* (Ahvonen, Sievers and Aho, 1969; Sievers, Ahvonen and Aho, 1972; Laitinen, Tuuhea and Ahvonen, 1972).
- iv) Venereally acquired non-specific urethritis (Csonka, 1958; Laird, 1958).

It is of interest to note that in the above studies of the arthritis associated with the three gastrointestinal infections a urethritis may occur in which case the affected patients are considered to have had Reiter's syndrome. If no urethritis occurred then the term reactive arthritis has been used. The clinical features of the arthritis, however, do not appear to differ in these two groups of patients. It is possible, therefore, that the urethritis is a variable clinical feature resulting from gastrointestinal infection in much the same way as the conjunctivitis which is not

a constant feature in Reiter's syndrome. Although non-specific urethritis is generally considered to be a venereally acquired infection it is of interest to note that in his review of this disease Csonka (1965) found that not all such patients had experienced extramarital sexual intercourse. In one series he reviewed, as many as 23% of patients denied such exposure. In addition not all patients with Reiter's syndrome have evidence of urethritis (Csonka, 1958). It would, therefore, seem reasonable to consider patients with a typical arthritis to have essentially the same disease whether urethritis is present or not when a precipitating gastrointestinal infection has recently occurred.

The finding of an association between these diseases and HLA-B27 (Table 6.3) irrespective of the presence of urethritis supports the view that similar genetic factors are present. If the frequency of the reactive arthritis for any one of these infections is known it is possible to estimate the prevalence of arthritis in HLA-B27 positive individuals. Alternatively in any one area it may be possible to determine the prevalence of arthritis in HLA-B27 positive individuals directly. Since all have been exposed to the particular environmental agent then a prevalence of disease in less than 100% of HLA-B27 positive individuals will be the result of genetic factors or possibly the result of insufficient antigenic load in some infected individuals for the arthritis to ensue.

Table 6.3 Frequency of HLA-B27 in reactive arthritis and Reiter's syndrome in reported series.

Reactive arthritis or Reiter's syndrome	Series	Frequency (%) of HLA-B27	
		in patients	in controls
Salmonella arthritis	1	60	8.1
	2	69.2	10.1
	3	94	14
Shigella arthritis	3	85	14
Yersinia arthritis	3	88	14
	4	65	14
Non-specific urethritis	5	75.8	6.1
	6	95.8	8.1
	7	80.4	4.0
	8	64.6	8.1
	9	71.4	8.2

1. Friis and Svejgaard (1974)
2. Hakansson et al (1975)
3. Aho et al (1975)
4. Leirisalo, Laitinen and Tiilikainen (1977)
5. Brewerton et al (1973b)
6. Morris et al (1974a)
7. Amor et al (1974)
8. Zachariae et al (1975)
9. Present series

Data are not available for *Yersinia* arthritis. Table 6.4 shows the prevalence of arthritis found or estimated in HLA-B27 positive individuals. These figures are based on relatively small numbers of patients. The estimate of Hakansson et al (1975) is based on one outbreak of Salmonellosis in southern Sweden in 1974, a total of 13 patients with arthritis being derived from a reported 330 of salmonellosis. The lower prevalence estimate of 11.9% by Friis and Svejgaard (1974) for arthritis in salmonellosis is based on patients admitted to hospital. It is possible that mild cases of arthritis were not admitted and so were not included resulting in a low estimate. The prevalence found by Hakansson et al (1975) could be artificially high if mild examples of salmonellosis who did not develop arthritis remained undiagnosed. It would seem probable that the true prevalence of arthritis following salmonella typhimurium infection lies somewhere between these two figures of 11.9% and 27%.

The estimated prevalence of arthritis in 20.6% of individuals with Shigellosis is based on a follow-up (Calin and Fries, 1976) of the U.S. Naval epidemic reported by Noer (1966). The number of affected individuals is small and the follow-up incomplete. No more satisfactory estimate, however, is available at the present time.

The prevalence figures derived from Laird (1958) and Csonka (1958) are based on their estimated prevalences

Table 6.4 Prevalence of reactive arthritis and Reiter's syndrome in HLA-B27 positive individuals infected with *Salmonella typhimurium*, *Shigella flexner* and in males with presumed venereally acquired non-specific urethritis.

Infecting agent	Study	Percent of individuals with reactive arthritis or Reiter's syndrome
<i>Salmonella typhimurium</i>	1	27.0
	2	11.9
<i>Shigella flexner</i>	3	16 - 37
Venereally acquired non-specific urethritis	4	15.9
	5	7.9
	6	20.0

1. Hakansson et al (1975)
2. Friis and Svejgaard (1974)
3. Calin and Fries (1976)
4. Laird (1958)
5. Csonka (1958)
6. Keat et al (1978)

for Reiter's syndrome in males with non-specific urethritis derived from their experience in two large London venereal clinics assuming an 8% frequency of HLA-B27 in males with non-specific urethritis. A possible reason for the two-fold difference in the estimated prevalence of Reiter's syndrome in HLA-B27 positive males is that Csonka (1958) included all examples of urethritis, gonococcal and non-gonococcal for his own estimates, whereas Laird (1958) excluded patients with gonococcal urethritis. It is of interest that the later, more direct estimate of Reiter's syndrome in HLA-B27 positive males with non-specific urethritis (Keat et al, 1978) gives a figure slightly higher than that derived from Laird (1958).

It would appear from the results of these various estimates of the prevalence of arthritis in HLA-B27 positive individuals exposed to two specific gastrointestinal infection and one venereal disease that this prevalence is similar in each of the three diseases and is in the region of 20% if allowance is made for the small numbers and methodology of some of the studies. Whilst it is not possible to be certain that the overall estimated prevalence is totally correct it is unlikely that the true prevalence will differ markedly from 20%.

As indicated previously a prevalence of arthritis in less than 100% of HLA-B27 positive individuals exposed to exogenous agents known to produce the arthritis suggests that not all HLA-B27 positive individuals are genetically

identical regarding genetic susceptibility to the arthritis. Two explanations are possible:

- i) The gene causing susceptibility to the reactive arthritis is in the major histocompatibility region but is not HLA-B27, i.e. a gene in linkage disequilibrium with HLA-B27 and occurs on only 20% of HLA-B27 positive chromosomes.
- ii) There is a gene in the major histocompatibility region which is HLA-B27 itself or a gene in marked linkage disequilibrium with HLA-B27 and usually present when the gene for HLA-B27 is present, but in addition a second independently segregating gene present in 20% of random individuals is necessary for the development of the arthritis in an exposed individual.

In the present series one family (P.14) was seen in which a patient with Reiter's syndrome had a relative with ankylosing spondylitis. In addition, Woodrow, Treanor and Usher (1974) had previously seen a further four similar families. In each of the five families in which genotyping of the affected individuals was possible it was found that they shared the same HLA-B27 positive haplotype. This suggests, whether the disease susceptibility gene is for HLA-B27 itself or a gene in linkage disequilibrium with HLA-B27, that it is the same gene in the major histocompatibility region which has predisposed one individual to develop Reiter's syndrome and a relative to develop ankylosing spondylitis. The traditional view that in patients with both ankylosing

spondylitis and Reiter's syndrome their ankylosing spondylitis arises as a consequence of their Reiter's syndrome (Ford, 1953; Csonka, 1958; Csonka, 1959; Oates, 1959; Good, 1965) is put into question by such families. In addition in the present series two males with their first episode of Reiter's syndrome were seen who clearly had symptomatic and radiological evidence of chronic disease of the sacroiliac joints prior to the development of their Reiter's syndrome. Woodrow, Treanor and Usher (1974) also found patients where ankylosing spondylitis ante-dated their Reiter's syndrome. This suggests that each disease has developed independantly of the other in individuals genetically susceptible to both, the common factor being the presence of HLA-B27.

6.3 PREVALENCE OF DISEASE IN HLA-B27 POSITIVE INDIVIDUALS

A common genetic factor in the major histocompatibility region predisposing to both Reiter's syndrome and ankylosing spondylitis allows comparison of the prevalence of arthritis in HLA-B27 positive individuals exposed to specific infections and the prevalence of ankylosing spondylitis in HLA-B27 positive males (Section 6.1.2). Whilst the possibility of environmental factors could be entertained for the lack of all HLA-B27 positive males developing ankylosing spondylitis, such an explanation is not possible for reactive arthritis and Reiter's syndrome, where it is known that not all HLA-B27 positive individuals exposed to the exogenous agent have developed

the arthropathy. The similarities in the proportion of HLA-B27 positive individuals developing Reiter's syndrome, reactive arthritis or ankylosing spondylitis suggests that if an environmental factor is necessary for the development of ankylosing spondylitis, then it is common and likely to affect most people at some time. Hence, the same two possible genetic explanations for the lack of development of arthritis in all HLA-B27 positive individuals exposed to infection known to result in reactive arthritis or Reiter's syndrome would equally apply to the lack of development of ankylosing spondylitis in all HLA-B27 positive males.

6.3.1 Relatives of probands with ankylosing spondylitis

Family studies of ankylosing spondylitis could give useful information in deciding which of these two explanations is more likely to be correct. If the gene predisposing to ankylosing spondylitis in linkage disequilibrium with those for HLA-B27 occurs in only 20% of HLA-B27 positive individuals then, assuming all family members have been exposed to the necessary environmental factor, it would be expected that all HLA-B27 positive male relatives of an HLA-B27 positive male with ankylosing spondylitis would have the same disease. In addition one would expect to see examples of familial ankylosing spondylitis in families where HLA-B27 is absent, the linked gene being on a non HLA-B27 positive chromosome. Equally the occasional example of a genetic recombinant between the gene for HLA-B27 and the disease susceptibility gene would be expected.

If HLA-B27 is the disease predisposing gene in the major histocompatibility region but a second independently segregating gene is necessary for the development of disease then one would expect to see only 50% of HLA-B27 positive male relatives of HLA-B27 positive patients with ankylosing spondylitis affected. In addition examples of genetic recombination would not occur between the gene for HLA-B27 and the disease predisposing gene, and familial examples of ankylosing spondylitis would not be expected in families lacking HLA-B27 if these two interacting genes were both necessary for disease development.

In the analysis of unselected parents of 23 HLA-B27 positive probands with ankylosing spondylitis 28.6% of fourteen HLA-B27 positive fathers were found to have the disease. This is considerably less than the 100% expected if a single linked gene in the major histocompatibility region were the only predisposing genetic factor. It is unlikely that many of the unaffected HLA-B27 positive fathers without ankylosing spondylitis will develop the disease in the future as they were all over the age of 40 years. Examination of the figures of Emery and Lawrence (1967), assuming all probands and affected relatives with ankylosing spondylitis in those families in which multiple cases occurred to be HLA-B27 positive, would suggest that 14% of HLA-B27 positive male first degree relatives had the disease. Making similar assumptions the figures of

de Blécourt, Polman and de Blécourt-Meindersma (1961) yield an estimated prevalence in HLA-B27 positive first degree male relatives of 12.8%. The lower figures in these two studies compared with the present study could be the result of the inclusion of siblings and offspring in their overall prevalence figures for relatives. It is possible that these unaffected younger relatives could develop the disease in the future.

If the two fathers with radiological sacroiliitis alone are included in the total obtained in the present study from the study of parents an overall prevalence of radiological sacroiliitis of 42.9% is found in HLA-B27 positive fathers. This can be compared with the 39.1% of HLA-B27 positive male first degree relatives which can be estimated from the figures of Emery and Lawrence (1967) using the above assumptions. It should be noted, however, that the estimated prevalence of radiological sacroiliitis in control HLA-B27 positive males would be 61.5% if a population prevalence for HLA-B27 of 8% is assumed. The reading of radiographs of the sacroiliac joints is notoriously difficult, especially in adolescent pelves (MacRae, Haslock and Wright, 1971), and such difficulties could be an explanation of the unexpectedly high estimated prevalence of radiological sacroiliitis in HLA-B27 positive controls compared with similar first degree relatives from the results of Emery and Lawrence (1967). Both this estimated prevalence of radiological sacroiliitis and that found in the present study are considerably smaller than

100% (for the present study $p < 0.01$).

One example of a genetic recombinant between HLA-B27 and a possible linked disease predisposing gene has been reported by Dick et al (1974). The only known example of a family in which two HLA-B27 negative first degree relatives have developed ankylosing spondylitis is pedigree P.26 of the present study. In the absence of more definite evidence for a linked disease producing gene in the major histocompatibility region it would be unwise to consider these as examples of the presence of such a gene (see Section 6.4).

The 28.6% prevalence of ankylosing spondylitis in the HLA-B27 positive fathers of probands with ankylosing spondylitis is approximately half that expected if the second hypothesis of a second independantly segregating gene present in 20% of random individuals were true. The upper 95% confidence limit for this prevalence is 58.1% which includes the 50% expected if this hypothesis is true. The 42.9% prevalence for radiological sacroiliitis in HLA-B27 positive fathers in the present study is nearer to the 50% expected as is the estimated prevalence of radiological sacroiliitis of 39.1% in HLA-B27 positive first degree male relatives from the figures of Emery and Lawrence (1967). Radiological sacroiliitis, however, cannot necessarily be equated with ankylosing spondylitis in the present context as Calin et al (1977a) found an additional 12 males with radiological abnormal sacroiliac joints in their follow-up of HLA-B27 positive asymptomatic blood donors, which would considerably increase the population prevalence of

disease based on radiological sacroiliitis in HLA-B27 positive males.

The expected prevalence of ankylosing spondylitis in HLA-B27 positive male relatives of 50% based on the hypothesis of a second independently segregating gene assumes that this is a single dominant gene, but there is no reason to believe this assumption is valid. It is possible that the hypothetical part of the genome predisposing to ankylosing spondylitis and independent of the major histocompatibility locus could be more than one independent gene which could be dominant or recessive. The above analysis does not allow differentiation between these possibilities but does support the possibility of an additional gene or genes independent of the major histocompatibility region being necessary for the development of ankylosing spondylitis.

One family in which the HLA-B27 negative son of a consanguineous mating had four HLA-B27 positive sons with ankylosing spondylitis has been reported (van der Linden et al, 1975). It has been suggested by the authors that this HLA-B27 negative male with ankylosing spondylitis could represent the result of disease in an individual homozygous for a recessive gene independent of the major histocompatibility region, all his HLA-B27 positive sons having developed the disease could represent the interaction of HLA-B27 with heterozygosity for this second hypothetical gene. It is of interest to note that the only example of two HLA-B27 negative first degree relatives with ankylosing spondylitis

(pedigree P.26) are the result of a consanguinous mating.

6.3.2 Comparison of the clinical features of ankylosing spondylitis in HLA-B27 positive and negative patients

If a predisposing gene for ankylosing spondylitis in the major histocompatibility region is HLA-B27 itself or a gene in marked linkage disequilibrium with HLA-B27 so that it is only rarely present in the absence of HLA-B27 then some clinical differences could be expected between HLA-B27 positive and negative patients with ankylosing spondylitis. If this disease is a result of a single gene in linkage disequilibrium with HLA-B27 then HLA-B27 negative patients would represent recombinants, having the disease predisposing gene but not HLA-B27, and could be expected to have a disease identical with their HLA-B27 positive counterparts.

Comparison of HLA-B27 positive and negative patients in the present series and others (section 5.1.2) suggests that differences may be present. HLA-B27 negative patients have a higher age of onset and more dactylitis of the toes; HLA-B27 positive patients have a higher risk of recurrent acute anterior uveitis.

6.4 THE ROLE OF GENES FOR PSORIASIS AND CHRONIC INFLAMMATORY BOWEL DISEASE IN ANKYLOSING SPONDYLITIS

The role of genetic factors in uncomplicated ulcerative colitis and Crohn's disease (Hammer et al, 1968) and psoriasis (Steinberg et al, 1951; Watson et al, 1971) is clearly established. In addition those same genetic factors have been shown to have a role in

predisposing to ankylosing spondylitis and the other seronegative spondarthritides (Hammer et al, 1968; Haslock, 1973; Macrae and Wright, 1973; Moll and Wright, 1973b; Lawrence, 1974). The finding of an association between HLA-B27 and ankylosing spondylitis alone (Brewerton et al, 1973a; Schlosstein et al, 1973) and in association with ulcerative colitis (Brewerton et al, 1974), Crohn's disease (Nagant de Deuxchaisnes et al, 1974) and psoriasis (Brewerton et al, 1974) allows further examination of these genetic inter-relationships.

In the present series the frequency of HLA-B27 in patients with ankylosing spondylitis and peripheral psoriatic arthritis is significantly less than in patients with ankylosing spondylitis alone ($p = 6.7 \times 10^{-4}$). The results of the combined analysis show that the relative risk for HLA-B27 in patients with chronic inflammatory bowel disease and ankylosing spondylitis and for patients with ankylosing spondylitis and peripheral psoriatic arthritis is significantly less than for patients with ankylosing spondylitis alone (Figure 6.2). In addition the relative risk for HLA-B27 in patients with peripheral psoriatic arthritis is significantly less than in patients with additional ankylosing spondylitis. This suggests that HLA-B27 negative patients with chronic inflammatory bowel disease or peripheral psoriatic arthritis are at increased risk for the development of ankylosing spondylitis compared with HLA-B27 negative individuals who do not have these diseases. Such an increased risk for HLA-B27 negative

Figure 6.2 A graphic representation of Y , the natural logarithm of the combined relative risk (X), and the 95% confidence limits of Y for HLA-B27 and ankylosing spondylitis alone, with psoriasis, peripheral psoriatic arthritis and chronic inflammatory bowel disease.

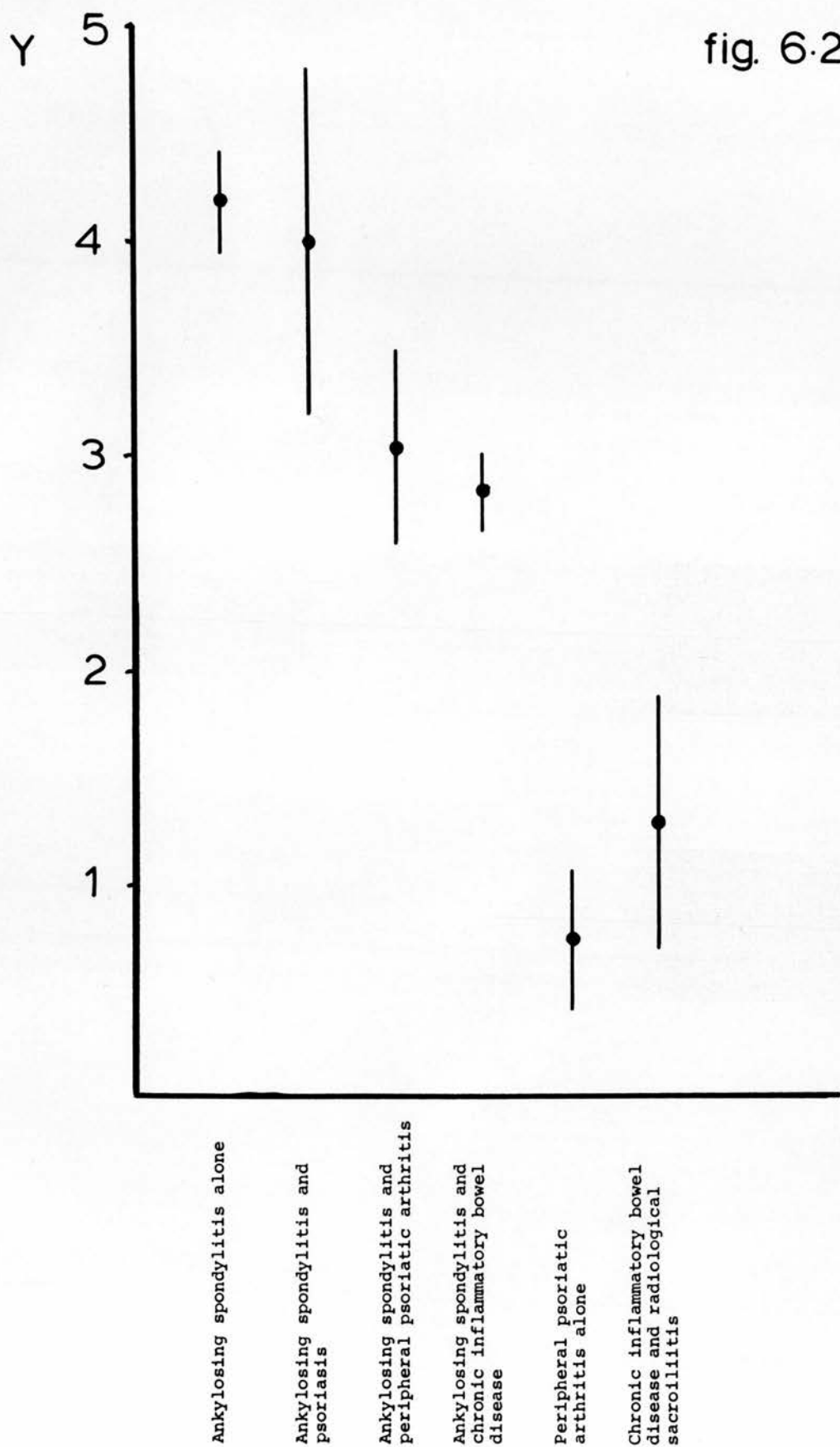


fig. 6.2

patients with chronic inflammatory bowel disease and peripheral psoriatic arthritis suggests that genetic or environmental factors predisposing to the development of these diseases also have a predisposing affect for the development of ankylosing spondylitis in the absence of HLA-B27. In the absence of knowledge of specific environmental factors in the aetiology of chronic inflammatory bowel disease and peripheral psoriatic arthritis it is difficult to examine the role of such factors in the development of ankylosing spondylitis. It is of interest to note that the combined relative risk for HLA-B27 in patients with psoriasis and ankylosing spondylitis without peripheral arthritis is very similar to that for patients with ankylosing spondylitis without psoriasis. In addition the frequency of HLA-B27 in patients with ankylosing spondylitis with and without psoriasis alone in the present series was found to be almost identical. This suggests that in patients with psoriasis but without peripheral psoriatic arthritis, predisposing factors for psoriasis have not led to an increased risk for the development of ankylosing spondylitis in HLA-B27 negative individuals. The combination of psoriasis and ankylosing spondylitis in patients without peripheral arthritis could represent the coincidence of these two diseases. The proband (II_2) of pedigree P.15 could represent such coincidental disease, inheriting his predisposition to ankylosing spondylitis from his father (I_1) and to psoriasis from his mother (I_2).

If genes predisposing to the development of chronic

inflammatory bowel disease or peripheral psoriatic arthritis are important in the development of ankylosing spondylitis in HLA-B27 negative patients with these diseases it could be expected that some HLA-B27 negative patients with ankylosing spondylitis alone would show evidence of such genes either in themselves or their relatives.

In the present series three male HLA-B27 negative patients with ankylosing spondylitis were seen who had small joint arthropathies with features suggestive of peripheral psoriatic arthritis (Cases 4.1(ii) - 4.1(iv)). In addition one HLA-B27 negative male had an acute peripheral arthritis with skin lesions of the type seen in pustular psoriasis or keratoderma blenorrhagica but without urethritis. This could be interpreted as an episode of Reiter's syndrome without urethritis or an acute resolving psoriatic arthritis. It is of interest to note that Lawrence (1974) found psoriasis as frequently in relatives of patients with Reiter's syndrome as in relatives of psoriatic arthritis suggesting that genetic factors predisposing to the development of psoriasis also may have a role in the development of Reiter's syndrome. Dactylitis of the toes, a common feature of psoriatic peripheral arthritis and Reiter's syndrome was seen significantly more frequently ($p = 3.5 \times 10^{-5}$) in HLA-B27 negative than HLA-B27 positive patients with ankylosing spondylitis. These findings regarding the type of peripheral arthritis which was seen in some patients with ankylosing spondylitis who were HLA-B27

negative suggests that factors normally predisposing to the development of psoriasis may have predisposed them to the development of ankylosing spondylitis in the absence of HLA-B27. Since they had no evidence, when examined, of psoriasis nor any history suggestive of this condition it is more probable that these "psoriatic factors" are of genetic rather than environmental origin.

Not only did case 4.1(iv) have features of peripheral psoriatic arthritis but his father (I_1 , pedigree P.16) had definite peripheral psoriatic arthritis without clinical or radiological evidence of spinal or sacroiliac disease. This family could represent the role of genes outwith the major histocompatibility region predisposing to peripheral psoriatic arthritis in the father (I_1 , pedigree P.16) and to ankylosing spondylitis in his son (II_2 , pedigree P.16). Not all examples of peripheral psoriatic arthritis in relations have been found in HLA-B27 negative probands with ankylosing spondylitis (pedigree P.17). Since HLA-B27 positive individuals have an increased risk of developing both ankylosing spondylitis and peripheral psoriatic arthritis it is possible in these families that the presence of HLA-B27 has predisposed to both peripheral psoriatic arthritis and ankylosing spondylitis in different members of the same family.

The results obtained from these unselected families can only hint at the possible genetic factors operating, but taken in conjunction with the clinical features of

the peripheral arthritis in patients with ankylosing spondylitis alone suggest that in HLA-B27 negative patients there is some evidence for genes predisposing to peripheral psoriatic arthritis also predisposing to the development of ankylosing spondylitis.

Unlike psoriasis there is no clinical feature in chronic inflammatory bowel disease which may occur independantly of this bowel disease as the peripheral arthritis of psoriasis may do. Enteropathic synovitis is not associated with an increased frequency of HLA-B27 in patients with chronic inflammatory bowel disease (Mallas et al, 1976; Dekker-Saeys et al, 1978b). The joint distribution of this arthritis is similar to that of the peripheral arthritis of ankylosing spondylitis (Wright and Moll, 1976). This makes distinction between these two types of peripheral arthritis by distribution impossible unlike the peripheral arthritis of psoriatic arthritis with its more characteristic small joint distribution.

One family (Pedigree P.26) in the present series shows an HLA-B27 negative proband (IV_2) with a HLA-B27 negative sister (IV_1) with both ulcerative colitis and ankylosing spondylitis and a mother (III_2) with ulcerative colitis alone. It is possible that genes normally predisposing to ulcerative colitis have also predisposed to the development of ankylosing spondylitis in both the sister with ulcerative colitis (IV_1) and her brother (IV_2) with ankylosing spondylitis alone. Since their parents (III_1 and III_2) are related

it is possible that these offspring (IV_1 and IV_2) are homozygous for some genes. It is of interest to note that in a series of 18 patients with ankylosing spondylitis (Lockshin et al, 1975) one HLA-B27 negative patient subsequently developed ulcerative colitis and Good, Kawanishi and Schultz (1976) saw an HLA-B27 negative patient with ankylosing spondylitis who had symptoms suggestive of Crohn's disease. No HLA-B27 negative patient with ankylosing spondylitis alone in the present series had symptoms suggestive of chronic inflammatory bowel disease.

These results suggest that in some HLA-B27 negative patients with ankylosing spondylitis alone genes normally predisposing to chronic inflammatory bowel disease have predisposed to the development of ankylosing spondylitis in the absence of bowel disease itself.

There is an increased prevalence of ankylosing spondylitis in patients with chronic inflammatory bowel disease (Ansell and Wrigley, 1964; Wright and Watkinson, 1965; Wright et al, 1965; Haslock, 1973; Macrae and Wright, 1973; Hyla, Frank and Davis, 1976) and since these diseases themselves are not associated with HLA-B27 (Hyla, Frank and Davis, 1976; van den Berg-Loonen et al, 1977; Morris et al, 1974b; Mallas et al, 1976) then either HLA-B27 positive patients with chronic inflammatory bowel disease have a higher risk for the development of ankylosing spondylitis than individuals without bowel disease, or factors related to

the development or presence of the bowel disease themselves must predispose to the development of ankylosing spondylitis. Since patients with chronic inflammatory bowel disease do not themselves have an increased frequency of HLA-B27 their relatives would also be expected to have a normal frequency of HLA-B27. The presence of an increased prevalence of ankylosing spondylitis in the relatives of patients with chronic inflammatory bowel disease (Haslock, 1973; Macrae and Wright, 1973) suggests that ankylosing spondylitis is likely to develop in those HLA-B27 negative relatives more frequently than similar unrelated individuals. This is further evidence in favour of genetic factors normally predisposing to the development of chronic inflammatory bowel disease also predisposing to the development of ankylosing spondylitis in the absence of clinical bowel disease.

It is evident that the genetic predisposition to the development of ankylosing spondylitis is not due to a single gene in the major histocompatibility region. There is certainly an important gene in this genetic region having a major effect in predisposing to the development of the disease, but also there is some evidence in favour of the necessity for additional independent genes in HLA-B27 positive individuals and for the genes normally predisposing to chronic inflammatory bowel disease and peripheral psoriatic arthritis also predisposing to the development of ankylosing spondylitis particularly in HLA-B27 negative individuals.

Figure 6.3 is an attempt to represent this concept of the interaction of several genes with a gene in the major histocompatibility region.

If more than one gene may predispose to the development of ankylosing spondylitis it is necessary to reconsider the family reported by Dick et al (1974) as illustrating a genetic recombination between the gene for HLA-B27 and a disease predisposing gene for ankylosing spondylitis. It is possible that in the HLA-B27 negative proband of this family genes other than these in the major histocompatibility region have predisposed to the development of ankylosing spondylitis. During the present study a similar family was ascertained (pedigree P.25) in which the HLA-B27 negative proband (II_1) with ankylosing spondylitis had an HLA-B27 positive brother (II_2) also with ankylosing spondylitis. The proband (II_1), however, had ulcerative colitis in addition to his spinal disease. It could, therefore, be argued that the presence of genes normally predisposing to ulcerative colitis in the proband (II_1) have also predisposed to the development of ankylosing spondylitis. Their sister (II_3) had had uveitis and was also HLA-B27 negative. It should be noted that these three siblings do not have any single histocompatibility haplotype in common with each other, and so do not represent examples of a disease predisposing gene or chromosome lacking the HLA-B27 gene, but linked to another B-series allele.

Figure 6.3 A diagrammatic representation of the interaction of a gene in the major histocompatibility region with genes normally predisposing to peripheral psoriatic arthritis and chronic inflammatory bowel disease in the development of ankylosing spondylitis.

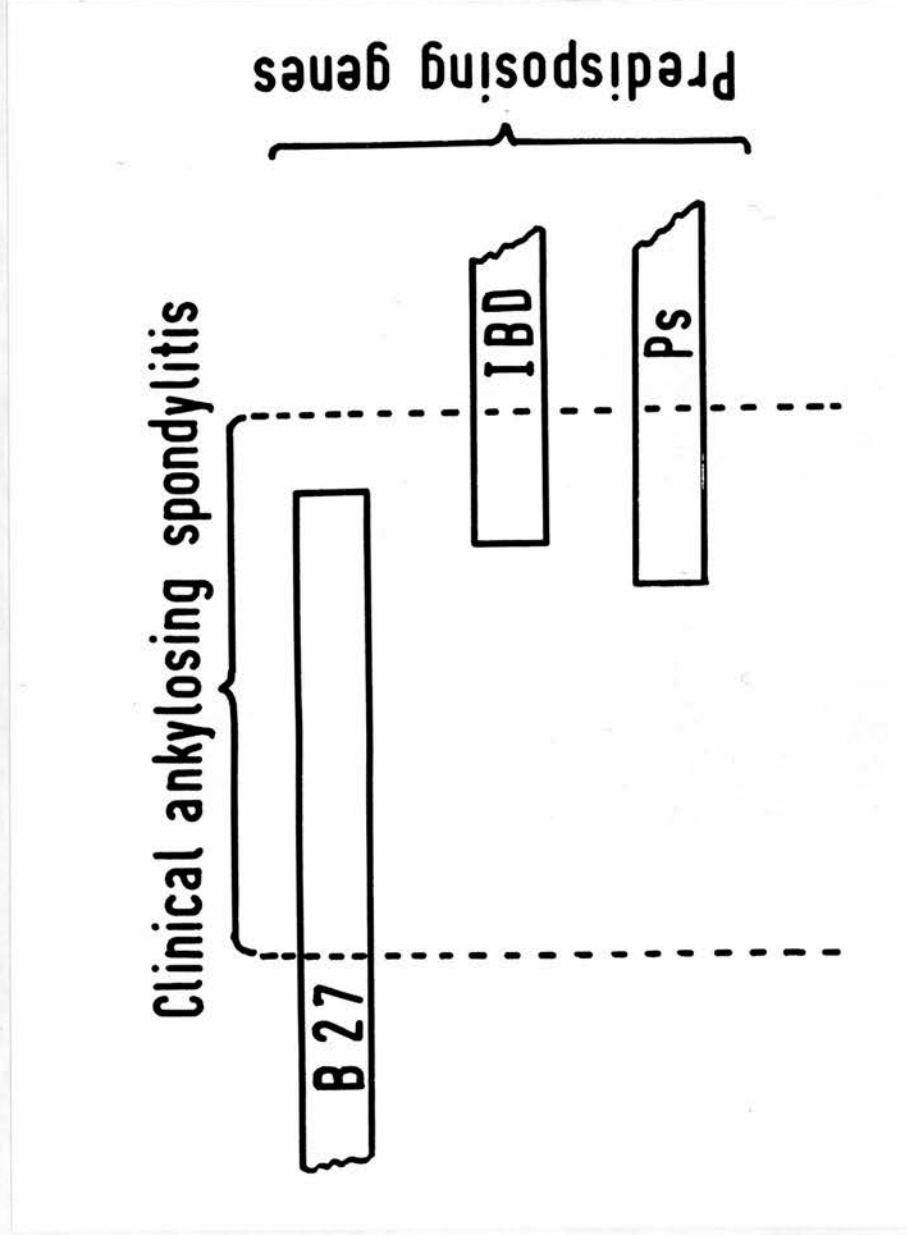
Clinical ankylosing spondylitis

B 27

IBD

Ps

Predisposing genes



6.5 FAMILIES WITH MULTIPLE EXAMPLES OF SERONEGATIVE SPONDARTHRTIDES

It has been argued (Section 6.3) on the basis of family studies that the disease predisposing gene in the major histocompatibility region is the same gene predisposing to both Reiter's syndrome and ankylosing spondylitis. Similar families were seen in which relatives with ankylosing spondylitis and peripheral psoriatic arthritis (pedigree P.17), ankylosing spondylitis with chronic inflammatory bowel disease (pedigrees P.22, P.21, P.23 and P.24), and acute anterior uveitis (pedigree P.27) had identical HLA-B27 haplotypes. This suggests that the gene in the major histocompatibility region predisposing to each of these disorders individually, as evidenced by the association of these individual diseases with HLA-B27, is likely to be the same gene. It is possible that this gene could be the gene for HLA-B27 or a linked gene. There is no conclusive evidence from the present or other studies in favour of either possibility. Three families (pedigrees P.28, P.29 and P.34) are of special interest in this respect. In two of these (pedigrees P.28 and P.29) teenage boys had a lower limb large weight bearing joint oligoarthritis similar to that seen in ankylosing spondylitis or Reiter's syndrome and reactive arthritis, and had fathers with ankylosing spondylitis. The affected members of these two families had inherited the same HLA-B27 haplotype. In the third family (pedigree P.34) the 26 year old son of a lady with uveitis

had symptoms restricted to the peripheral entheses of the heels and had inherited the same HLA-B27 haplotype as his mother. During the course of this study a further 15 patients were seen (Section 4.7) with a similar peripheral arthritis or arthropathy of whom 77.8% were HLA-B27 positive. It is known that patients subsequently developing ankylosing spondylitis may have their early symptoms confined to a peripheral joint (Tyson, Thompson and Ragan, 1953; Hart and MacLagan, 1955; Wilkinson and Bywaters, 1958; Hart and Robinson, 1959; Riley, Ansell and Bywaters, 1971; Ladd, Cassidy and Martel, 1971). This is especially the case in patients who have their initial symptoms in their teens (Riley, Ansell and Bywaters, 1971; Ladd, Cassidy and Martel, 1971). It is possible that the patients with these peripheral joint symptoms seen during the present study may ultimately develop ankylosing spondylitis. Fletcher and Scott (1975), however, in their follow-up of 151 patients initially presenting with a monoarthritis saw 49 (32%) for whom no cause was ultimately found and in all these except a very small minority total remission occurred. They do not give any details of histocompatibility testing in these patients but it is possible that they were similar to patients seen in the present study and those of Keat and Barnes (1976) and Arnett et al (1978) in whom a high frequency of HLA-B27 was found.

It has been shown that patients initially presenting the features of juvenile chronic arthritis who subsequently

develop ankylosing spondylitis have an increased frequency of HLA-B27 (Edmonds et al, 1974; Hall et al, 1975; Veys et al, 1976). In their study Hall et al (1975) found the HLA-B27 positive patients to have fewer joints involved and these mainly of the lower limb. Not all these patients had developed ankylosing spondylitis. It would appear that teenage HLA-B27 positive males have an increased risk of developing a lower limb oligoarthritis, including an enthesopathy of the heel, but that not all such affected will ultimately develop ankylosing spondylitis. In the absence of any other specific feature, such as radiological sacroiliitis, acute anterior uveitis or a family history of a seronegative spondarthrititis it is possible that histocompatibility testing could be of diagnostic value in this group of patients.

CONCLUSIONS

1. An association between the histocompatibility antigen HLA-B27 and
 - (a) ankylosing spondylitis alone or associated with chronic inflammatory bowel disease or psoriasis and peripheral psoriatic arthritis
 - (b) Reiter's syndrome
 - (c) reactive arthritis secondary to *Salmonella typhimurium*, *Shigella flexner* and *Yersinia enterocolitica*
 - (d) peripheral psoriatic arthritis
 - (e) acute non-granulomatous anterior uveitis
 - (f) certain forms of chronic juvenile arthritisis firmly established.
2. The prevalence of ankylosing spondylitis in HLA-B27 positive males of all racial groups is approximately 20% and the relationship between the prevalence of this disease and the frequency of HLA-B27 in any given population is given by $y = 0.19x + b$ where y is the prevalence of ankylosing spondylitis, x is the frequency of HLA-B27 in the same population and b is a small number (the present analysis giving a value of -0.039).
3. The prevalence of Reiter's syndrome and reactive arthritis in HLA-B27 positive individuals infected is approximately 20%.
4. There is evidence for the necessity of a gene or genes segregating independantly of the major histocompatibility region in addition to a gene in that region for the development of ankylosing spondylitis.

5. Genes normally predisposing to chronic inflammatory bowel disease and peripheral psoriatic arthritis may in addition predispose to the development of ankylosing spondylitis particularly in HLA-B27 negative individuals.
6. Environmental factors in addition to a genetic predisposition are probably necessary for the development of ankylosing spondylitis.
7. Histocompatibility testing may be of diagnostic value in young males presenting with an oligoarthritis affecting the weight bearing joints of the lower limbs.

SUGGESTIONS FOR FURTHER STUDIES

The results of these studies suggest four major areas for further research. The data on which the linear correlation between the population frequency of HLA-B27 and prevalence of ankylosing spondylitis has been demonstrated is based on only a small number of relatively imprecise studies particularly with regard to the prevalence of ankylosing spondylitis. It would be of considerable value to know more accurately the population prevalence of ankylosing spondylitis in several populations using epidemiological techniques to determine if there is indeed a linear relationship with the frequency of HLA-B27 in the populations. The slope of the resulting regression line would then give the proportion of HLA-B27 individuals developing the disease.

A more direct way of obtaining this information in any one population could be to look at apparently healthy HLA-B27 positive individuals. Comparison of the number of random HLA-B27 positive individuals with disease should be compared with first degree relatives, both parents and siblings, of unselected probands with ankylosing spondylitis and other seronegative spondarthritides using identical study methods. A major deficiency of the comparisons made in the present study was the result of being unable to examine histocompatibility type blood donors. Since the completion of this work such a study has been commenced by Dr. J. C. Woodrow in Liverpool. The results of such an investigation should provide important information regarding the possibility of the necessity for additional genes outwith the major histocompatibility region.

The present series has brought attention to a group of patients with a seronegative oligoarthritis predominantly affecting the weight bearing joints. Some may be considered to be examples of juvenile oligoarthritis liable subsequently to develop ankylosing spondylitis. The majority, however, had an onset in adult life. Detailed study of a larger group of such patients with careful follow-up with regard to the subsequent development of other seronegative spondarthritides would be of interest and value and not least in obtaining accurate prognostic information for this disorder.

Further study is indicated into the possibility of interaction of a gene in the major histocompatibility region and environmental factors in the development of ankylosing spondylitis. From further studies completed since the writing of this thesis there is some evidence that *Klebsiella aerogenes* in the bowel flora is not associated with ankylosing spondylitis itself but with its associated uveitis (Eastmond et al, 1979; Ebringer et al, 1979).

Footnote: Eastmond, C.J., Wilshaw, H.E., Burgess, S.E., Shinebaum, R., Cooke, E.M. and Wright, V. (1979). The frequency of faecal *Klebsiella aerogenes* in patients with ankylosing spondylitis and controls with respect to individual features of the disease. *Annals of the Rheumatic Diseases* (in press).

Ebringer, R., Cawdell, D. and Ebringer, A. (1979). *Klebsiella pneumoniae* and acute anterior uveitis in ankylosing spondylitis. *British Medical Journal*, 1, 383.

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APPENDIX

PUBLISHED PAPERS

The HLA system and the arthropathies associated with psoriasis

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SUMMARY Histocompatibility typing was carried out in 74 patients with psoriasis and an inflammatory arthropathy. In 40 patients with peripheral arthropathy characterized by distal interphalangeal joint involvement, 13 (32.5%) were HLA-B27 positive, significantly higher than the control frequency ($P=5.8 \times 10^{-6}$). 26 of the 40 patients did not have ankylosing spondylitis or radiological sacroiliitis and 7 were HLA-B27 positive, also significantly higher than in controls ($P=0.004$). All 7 patients with psoriasis and ankylosing spondylitis without peripheral arthropathy were HLA-B27 positive. The 10 patients with ankylosing spondylitis or radiological sacroiliitis who were HLA-B27 negative all had peripheral arthropathy.

It is suggested that being HLA-B27 positive increases the risk of a psoriatic patient developing both peripheral arthropathy and ankylosing spondylitis. In addition, some of the genes involved in susceptibility to psoriasis also have a role in the pathogenesis of both types of arthropathy. A hypothesis is put forward that some of the genes for psoriasis may be aetiologically important in some HLA-B27 negative patients with ankylosing spondylitis.

Following the reports of an association between the histocompatibility antigen HLA-B27 and ankylosing spondylitis by Brewerton *et al.* (1973) and Schlosstein *et al.* (1973) there have been a number of studies reporting on the frequency of this antigen in what Wright has termed the seronegative spondyloarthritides (Wright and Moll, 1973). Several studies of psoriatic arthropathy show general agreement that there is an association between HLA-B27 and psoriasis with ankylosing spondylitis with or without peripheral arthropathy (e.g. Brewerton *et al.*, 1974; Karvonen, 1975). There is, however, no agreement concerning the frequency of this antigen in the absence of spinal involvement. Some workers have claimed an association (Brewerton *et al.*, 1974; Karvonen, 1975), while others claim no association (Sany *et al.*, 1975).

One of the problems with such a study is the definition of the clinical entity to be studied. Sany *et al.* (1975) included patients who were seropositive for rheumatoid factor, and the criteria used by Metzger *et al.* (1975) for radiological spondylitis could have included patients with and without sacroiliitis. Moll and Wright (1973a) identified four types of peripheral arthropathy related to psoriasis.

They were (1) a polyarthritis characterized by distal interphalangeal joint involvement, (2) mutilating arthritis with telescoping digits, (3) a symmetric seronegative polyarthritis, and (4) an asymmetric oligoarthritis including 'sausage digits'. Because of the heterogeneity of the clinical picture in psoriatic arthropathy we decided to HLA type all patients referred to us who had psoriasis with an inflammatory peripheral arthritis and to categorize them subsequently independent of the knowledge of their HLA type. We also studied a group of patients who had ankylosing spondylitis with or without peripheral arthropathy.

Patients

The patients either were attending our own clinic or were referred to us by colleagues for study. All were examined by one or both of us. Patients with peripheral arthropathy involving the hands and feet had radiographs of these joints and in addition anteroposterior and lateral radiographs of the spine, posteroanterior view of the sacroiliac joints, and anteroposterior view of the pelvis. Spinal, sacroiliac and pelvic radiographs were not done in females under the age of 45 years who did not have back symptoms.

Table 1 Number of patients with psoriatic arthropathy in each clinical group

Clinical groups	Peripheral joint disease alone		With sacroiliitis		With spondylitis without sacroiliitis		Sacroiliitis not known		Total no.	
	M	F	M	F	M	F	M	F	M	F
Peripheral arthritis										
Group 1	11	12	6	3	3	—	—	5	20	20
Groups 2, 3, and 4	—	3	3	5	—	1	—	—	3	9
Group 5	1	—	4	—	—	—	1	1	6	1
Group 6 (a) seropositive	1	3	—	—	—	—	—	—	1	3
(b) seronegative	1	1	—	—	—	—	—	—	1	1
Spondylitis										
Ankylosing spondylitis	—	—	6	1	—	—	—	—	6	1
Spondylitis without sacroiliitis	—	—	—	—	2	—	—	—	2	—
Total	14	19	19	9	5	1	1	6	39	35

PERIPHERAL ARTHROPATHY

Of the patients with peripheral arthropathy and psoriasis seen during this study we have been able to identify the following groups (Table 1).

Group 1

Forty patients with peripheral arthropathy characterized by distal interphalangeal involvement alone as part of a polyarthritis (DIP disease).

Group 2

Five patients with a polyarthritis differing clinically from rheumatoid arthritis but not having definite DIP joint involvement. These patients are tabulated individually (Table 2).

Group 3

Two patients with a polyarthritis clinically indistinguishable from rheumatoid arthritis but with unusual radiological features (Table 2).

Group 4

One patient with arthritis mutilans, i.e. telescoping digits (Table 2).

Group 5

Seven patients with a monarthritis (in all cases a synovitis of the knee joint).

Group 6

Six patients with a polyarthritis clinically and radiologically indistinguishable from rheumatoid arthritis.

The patients in groups 2, 3, and 4 probably represent a heterogeneous group and it is for this reason that they have been tabulated individually. Sausage digits are probably the result of combined proximal and DIP joint involvement together with a flexor sheath tendonitis. Although DIP involvement is therefore implied, patients with sausage digits have not been included in group 1 unless DIP involvement

Table 2 Details of patients in groups 2, 3, and 4

Sex	Age	Family history of psoriasis	Nail involvement	Arthropathy							HLA type		
				Symmetry	Special features			Radiological features			Group†	A	B
					Sausage fingers	Toe involvement	Achilles tendonitis	Characteristic peripheral joint changes	Sacroiliitis	Syndesmophytes*			
F	49	+	+	—	+	—	—	—	—	—	2	1	w17,18
F	52	—	—	—	—	+	—	—	—	—	2	9,28	14,w16
F	59	—	—	+	—	—	—	+	—	—	3	3,11	w35,w17
F	67	—	—	+	+	—	—	—	—	NM	2	1,3	8,12
F	46	—	—	—	—	—	+	—	+	NM	2	1,2	13,27
F	42	—	+	+	+	+	—	—	+	—	2	1,3	27,w37
F	50	—	+	+	—	+	—	—	+	NM	2	1,10	12,w17
F	74	—	+	—	+	—	—	—	+	M	2	1,2	7,14
F	52	—	+	+	—	—	+	—	+	M	2	1,2	12,27
M	32	—	—	+	—	—	—	+	+	—	3	2,10	12,27
M	37	—	+	—	—	—	—	—	+	—	2	2,	7,12
M	73	+	+	—	—	—	—	—	+	M	4	3,11	w16,w35

* = marginal syndesmophytes; NM = nonmarginal syndesmophytes.

† see text.



Fig. 1 Radiograph of foot of Case 3 (group 3) showing whittling of the distal ends of the metatarsals.



Fig. 2 Radiograph of the index finger of Case 10 (group 3) showing destructive arthritis of the proximal interphalangeal joint with whittling of the distal end of the proximal phalanx.

as also occurred as a discrete event. In 2 of the patients in this group Achilles tendonitis was a feature and although it has been suggested that it occurs in rheumatoid arthritis (Bywaters, 1954) it is probably more characteristic of the seronegative spondyloarthritides. The radiographs of the 2 patients in group 3 are shown in Figs. 1 and 2. Case 10 is of interest because his peripheral arthropathy started at the age of 10 years, the symptoms of ankylosing

spondylitis at age 19 years, whereas psoriasis did not appear until he was 29 years old.

With regards to group 6, synovitis of the knee is a relatively nondiagnostic finding, occurring in a variety of inflammatory rheumatic disorders. Hence its occurrence in a patient with psoriasis does not necessarily mean that the monoarthritis is in any way related to the presence of psoriasis, though it may be. The problem of categorizing these patients is typified



Fig. 3 Anteroposterior radiograph of the lower lumbar spine of a patient with spondylitis without sacroiliitis showing nonmarginal syndesmophytes at L3,4,5 level laterally.

by such a patient who has subsequently developed typical nail dystrophy and DIP disease, and has now been included in this latter category. Similarly, patients who may subsequently develop ankylosing spondylitis may originally present with a monarthrititis, frequently of the knee, or this may occur after the development of spinal disease. It is for these reasons that we have analysed our data on patients with a monarthrititis of the knee separately from the other groups of peripheral arthropathy. 4 of the 6 patients in group 6 were seropositive for rheumatoid factor.

SPONDYLITIS

Ankylosing spondylitis

In addition to the patients with peripheral arthropathy, we also studied a group of 7 patients with ankylosing spondylitis without peripheral arthropathy (Table 1). Of the 28 patients with ankylosing spondylitis with and without peripheral arthropathy 14 had sacroiliitis alone, 8 marginal syndesmophytes and 6 nonmarginal syndesmophytes.

Spondylitis without sacroiliitis

Six patients (5 male, 1 female) were seen who ha



Fig. 4 Lateral radiograph of the cervical spine of the same patient illustrated in Fig. 3 to show florid non-marginal syndesmophytes anteriorly.



Fig. 5 Lateral radiograph of the cervical spine of the same patient as illustrated in Fig. 4, 3 years later.

radiological changes in the spine not conforming to ordinary degenerative changes and who did not have sacroiliitis (Table 1). 3 of the 6 had DIP disease and 2 were included in group 1 and one of these had changes similar to ankylosing vertebral hyperostosis. Another patient with similar radiological changes did not have peripheral joint disease, but complained of backache and stiffness. A further patient who also had DIP disease had changes on the right side of the lower dorsal spine similar to ankylosing hyperostosis but anteriorly the changes were more typical of non-marginal syndesmophytes. One other patient with DIP disease had a nonmarginal syndesmophyte anteriorly at the D12-L1 level. Another male patient with psoriasis who had no peripheral joint disease but complained of back pain and stiffness at the age of 35 years has now at the age of 47 years non-marginal syndesmophytes bridging the L3,4,5 discs laterally (Fig. 3) and the L3,4,5 spaces anteriorly. Over this period he has also developed nonmarginal syndesmophytes anteriorly throughout the cervical spine (Fig. 4) which have subsequently developed into a layer of new bone anterior to the cervical vertebrae (Fig. 5). The dorsal and upper lumbar spine are unaffected. The one female in this group is also in group 2. She has nonmarginal syndesmophyte formation at the C5,6,7 level, associated with pain in the neck.

FAMILY STUDIES

Each patient was asked if a first- or second-degree

relative had psoriasis. Selected families, where it was known that a relative had a seronegative arthropathy, were studied.

Histocompatibility typing

Histocompatibility typing was performed on all patients using a two-stage lymphocytotoxicity micromethod (Terasaki and McLelland, 1964). Control blood samples were obtained from 433 blood donors and members of staff.

Results

ASSOCIATION WITH HLA-B27 (TABLE 3)

Peripheral arthropathy

Group 1 13 of the 40 patients (32.5%) had HLA-B27 compared with 36 of our 433 controls (8.31%), giving $\chi^2_c = 20.54$; $P = 5.8 \times 10^{-6}$. 26 of the 35 patients who had pelvic radiographs had normal sacroiliac joints. 7 of these had HLA-B27 and compared with controls, $\chi^2_c = 7.93$; $P = 0.0049$. 9 patients had radiological sacroiliitis and 5 (55.6%) of these were HLA-B27 positive. Comparison with controls gives $\chi^2_c = 18.1$; $P = 2.1 \times 10^{-5}$. Of the 5 female patients who did not have sacroiliac radiographs, one was HLA-B27 positive.

Groups 2, 3, 4 Table 2 gives the clinical and radiological features and HLA phenotypes of the patients in these groups. It can be seen that all 3 male

Table 3 Frequencies of HLA-B27 and Bw17 in patients with psoriatic arthropathy, in patients with psoriasis, and in controls

Clinical groups	No. of patients	HLA-B27 positive		HLA-Bw17 positive	
		No.	%	No.	%
<i>Peripheral arthritis</i>					
Group 1	40	13	32.5	12	30.0
DIP disease alone	26	7	30.4	9	34.6
" + sacroiliitis	9	5	55.6	1	11.1
Groups 2, 3, and 4	12	4	33.3	3	25.0
Peripheral arthritis alone	4	0	0	2	50.0
" + sacroiliitis	8	4	50.0	1	12.5
Group 5	7	2	28.6	1	14.3
Peripheral arthritis alone	3	0	0	1	33.3
" + sacroiliitis	4	2	50.0	0	0
Group 6					
Seropositive RA	4	1	25.0	2	50.0
Seronegative RA	2	1	50.0	0	0
<i>Spinal disease</i>					
Ankylosing spondylitis (all)	28	18	64.3	2	7.1
" without peripheral arthropathy	7	7	100.0	0	0
Sacroiliitis without sacroiliitis	6	0	0	2	33.3
<i>Liverpool Psoriasis Series</i>					
Godrow and others (1975))	125	15	12.0	63	50.4
<i>Controls</i>	433	36	8.3	34	7.9

and 5 of the 9 female patients had radiological sacroiliitis and HLA-B27 was present in 4 of these 8 (50%), but did not occur in the 4 female patients without sacroiliitis.

Group 5 Of the 7 patients with a synovitis of the knee, 4, all male, had ankylosing spondylitis and 2 (50%) were HLA-B27 positive. The remaining 3 patients, 2 of whom were male, did not have this antigen.

Group 6 Of the 4 patients with seropositive rheumatoid arthritis, one had HLA-B27. Of the 2 seronegative patients in this group, one had HLA-B27.

Spondylitis

Ankylosing spondylitis Of the total of 28 patients (19 males, 9 females) with ankylosing spondylitis or radiological sacroiliitis, HLA-B27 was present in 18 (64.3%), and comparison with controls gives $\chi^2_c = 74.35$; $P = 6.5 \times 10^{-18}$. All 7 patients who had ankylosing spondylitis in association with psoriasis in the absence of any peripheral joint involvement were HLA-B27 positive. 6 of these were male and all had an age of onset of their back symptoms before the age of 40 years. In contrast, of the 21 patients who in addition had various forms of peripheral arthropathy, only 13 were male and of the 16 in

whom it was possible to ascertain the age of onset back symptoms with reasonable accuracy, 7 had an onset after the age of 40 years. 11 of these 21 patients were HLA-B27 positive, a frequency significantly less than the 90% found in a personal series of patients with ankylosing spondylitis without psoriasis ($\chi^2_c = 15.67$; $P = 7.5 \times 10^{-5}$).

Of the 10 patients with sacroiliitis who were B negative all had peripheral joint involvement; 4 in group 1, 3 in group 2, the one in group 4, and 2 in group 5. HLA-B27 was present in 8 of the patients with radiological sacroiliitis only, in 5 of the 8 patients with marginal syndesmophytes, and in 3 of the 6 with nonmarginal syndesmophytes. There were no significant differences between these groups in the frequency of HLA-B27.

Spondylitis without sacroiliitis None of the 10 patients with spondylitis in the absence of sacroiliitis were HLA-B27 positive.

OTHER HLA ANTIGENS

Because of the known association of psoriasis with HLA-Bw17 and B13 (White *et al.*, 1972), the frequencies of these two antigens in our patients with psoriatic arthropathy were also studied. The results for HLA-Bw17 are summarized in Table 1. There was a significant increase in the frequency

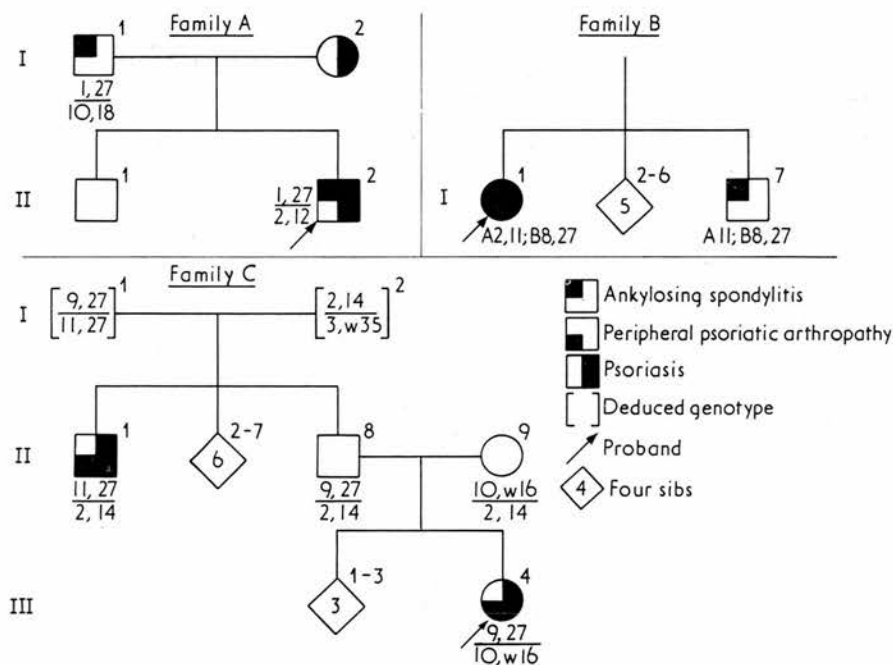


Fig. 6 Pedigrees families A, B, and C.

antigen in patients with peripheral arthropathy but not in those with ankylosing spondylitis.

Four patients were HLA-B13 positive. 3 of these had radiological sacroiliitis and were also HLA-B27 positive. The overall frequency of HLA-B13 in patients with sacroiliitis was 10.7%. One of these 3 patients had group 1 peripheral arthropathy, one (case 5) had group 2 peripheral arthropathy, and one had no peripheral arthropathy. The fourth HLA-B13 positive patient had group 1 peripheral arthropathy and was also HLA-Bw17 positive. The frequency of HLA-B13 in peripheral arthropathy was 5%, compared with 5.3% in healthy controls, and with 9.6% in unselected psoriatic patients in our pool (Woodrow *et al.*, 1975).

FAMILY STUDIES

A positive family history of psoriasis was obtained in 25 of the 75 (33.3%) patients with psoriasis and arthropathy and this is not significantly different from the frequency of 40.1% found in a general series of 157 psoriatic patients (Woodrow *et al.*, 1975). Three families are shown in Fig. 6. Family A shows an HLA-B27 positive proband who has ankylosing spondylitis and psoriasis, whose HLA-B27 positive father has ankylosing spondylitis but no psoriasis and whose mother has only psoriasis.

In Family B the brother of one of the HLA-B27 positive female patients (Case 9) with ankylosing spondylitis and group 2 peripheral arthropathy had himself ankylosing spondylitis without psoriasis but was HLA-B27 positive. Family C is of particular interest in that the proband and her paternal uncle both had group 1 peripheral arthropathy (DIP disease) and psoriasis. Both had a genotype including HLA-B27 but the haplotypes were different. The mother of the proband had neither ankylosing spondylitis nor psoriasis.

DISCUSSION

The results of this study show that there is a significant increase in the frequency of HLA-B27 in patients with DIP disease whether or not radiological sacroiliitis is present. This suggests that being HLA-B27 positive increases the risk of a psoriatic patient developing this type of arthropathy. In respect of the three types of peripheral arthropathy, although overall there is an increase in the frequency of HLA-B27, the fact that most of the patients also had ankylosing spondylitis or radiological sacroiliitis, the small numbers in each group make it difficult to determine whether or not HLA-B27 is associated with an increased risk of developing these forms of arthropathy.

Among the 28 patients with ankylosing spondylitis or radiological sacroiliitis were 7 who had no peripheral arthropathy. It is reasonable to expect that ankylosing spondylitis will occur as frequently in patients with psoriasis as in people without psoriasis simply by chance, and these 7 patients could represent such an occurrence. In support of this is the finding that all were HLA-B27 positive, all but one were male, and all had onset of back symptoms before the age of 40 years. This pattern is characteristic of any group of patients having ankylosing spondylitis in the absence of psoriasis. In Moll and Wright's (1973b) family study of 88 probands with psoriatic arthropathy there were 6 with ankylosing spondylitis and no peripheral arthropathy of whom only one was female.

In contrast the remaining 21 patients, all of whom had peripheral arthropathy in addition to ankylosing spondylitis or radiological sacroiliitis, also differed from the 7 patients without peripheral arthropathy in having a higher proportion of females, a tendency to a later age of onset of back symptoms and much lower frequency of HLA-B27. The frequency of HLA-B27 in this group is significantly less than that found in our own series of 116 patients with ankylosing spondylitis alone. These differences between the two groups of patients with psoriasis and ankylosing spondylitis or radiological sacroiliitis can be interpreted as suggesting that in the complex of genes predisposing to psoriasis are particular genes that cause susceptibility to both peripheral arthropathy and ankylosing spondylitis in the absence of HLA-B27.

Among 12 HLA-B27 negative patients in a series of 116 patients with ankylosing spondylitis without psoriasis, 3 had an inflammatory peripheral small joint arthropathy with clinical or radiological features identical with those seen in patients with peripheral psoriatic arthropathy. It seems possible, therefore, that genes for psoriasis may also play a role in the pathogenesis of some HLA-B27 negative patients with ankylosing spondylitis who do not have psoriasis. This hypothesis is illustrated in Table 4. It might also be speculated that these same genes for psoriasis might also result in the seronegative peripheral arthropathies without psoriasis seen by Moll and Wright (1973b) in the families of probands with psoriatic arthropathy.

Family A (Fig. 6) could be interpreted as representing the chance coincidence of HLA-B27 positive ankylosing spondylitis and psoriasis in the proband; his father having HLA-B27 positive ankylosing spondylitis alone, and his mother psoriasis alone. Family B (Fig. 6) may be interpreted in two ways. First, it could be that the proband's brother without psoriasis has HLA-B27 positive ankylosing spondy-

Table 4 Interpretation of the contributing genes in psoriatic arthropathy and some patients with HLA-B27 negative ankylosing spondylitis

	Type of arthropathy	Genes predisposing to arthropathy	
		Psoriasis genes	HLA-B27
Patients with psoriasis	Peripheral arthropathy alone	+	+
	Peripheral arthropathy with sacroiliitis	+	+
	Ankylosing spondylitis alone	—	+
Patients without psoriasis	HLA-B27 negative ankylosing spondylitis	+	—

litis, the proband having in addition genes for psoriasis predisposing to peripheral arthropathy. The second possibility is that HLA-B27 in the proband has increased her susceptibility to both peripheral arthropathy and ankylosing spondylitis in the presence of genes for psoriasis, whereas in her brother, in the absence of these genes, susceptibility was only increased for ankylosing spondylitis. Family C (Fig. 6) suggests that genes for psoriasis have interacted with two independently inherited HLA-B27 genes to predispose to DIP disease in 2 individuals.

Overall the frequencies of HLA-Bw17 and B13 are not significantly different from those found in a group of psoriatic patients not selected for arthropathy (Woodrow *et al.*, 1975), once allowance has been made for the increased frequency of HLA-B27 in those with arthropathy.

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Discordance for ankylosing spondylitis in monozygotic twins

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SUMMARY Three monozygotic twin pairs, each over the age of 45 years, with ankylosing spondylitis are described. In two pairs there is discordance for this disease and in the third pair there is a marked difference in the severity of this disease. These findings provide evidence that environmental factors are necessary not only for the initial development of ankylosing spondylitis, but possibly also for determining its future severity.

Genetic factors are known to be important in the aetiology of the seronegative spondylarthritides (Emery and Lawrence, 1967; Moll and Wright, 1973; Lawrence, 1974). The finding of an increased frequency of the histocompatibility antigen B27 in ankylosing spondylitis by Brewerton *et al.* (1973a) and Schlosstein *et al.* (1973) suggested that at least part of the genetic susceptibility to ankylosing spondylitis is due to genes in the HLA chromosomal region. Associations have also been found between HLA B27 and Reiter's syndrome (Brewerton *et al.*, 1973b; Woodrow *et al.*, 1974) and the reactive arthropathies (Aho *et al.*, 1973). While genetic factors are known to be important in predisposing to Reiter's syndrome (Lawrence, 1974) and the reactive arthropathies, there is also evidence that infective micro-organisms are necessary for the initial development of these diseases. Similar direct evidence of an environmental factor being necessary for the development of ankylosing spondylitis is

lacking. Moesmann (1960), reviewing the published data on monozygous twins and ankylosing spondylitis, found nine reported twin pairs of which three

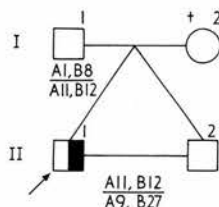


Fig. 1 Pedigree of family P showing discordance for ankylosing spondylitis in monozygotic twins.

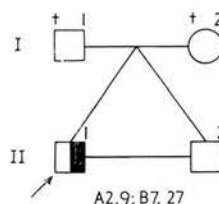


Fig. 2 Pedigree of family R showing discordance for ankylosing spondylitis in monozygotic twins.

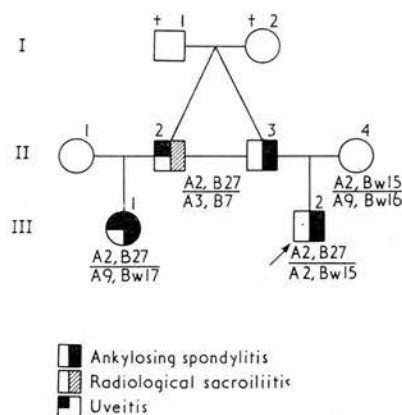


Fig. 3 Pedigree of family E showing concordance for radiological sacroiliitis and discordance for clinical ankylosing spondylitis and anterior uveitis in monozygotic twins.

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ere discordant for ankylosing spondylitis. Three further concordant pairs of monozygotic twins have been reported (Kuthan and Navratil, 1966; Ruog *et al.*, 1975). We report our findings on three pairs of monozygotic twins seen during the course of family studies of ankylosing spondylitis.

Patients and methods

Each twin had a full history and rheumatological

examination and radiographs of the sacroiliac joints were performed. Radiographs of the spine were taken where indicated. Blood samples were taken for multiple red blood cell grouping (ABO, Rhesus, MNS, P, Kell, Duffy, and Kidd) and HLA typing, which was performed by a microlymphocytotoxicity method (Teraski and McClelland, 1964). Other affected members of the twins' families were examined clinically and radiologically and blood taken for HLA typing.



Fig. 4 Radiologically normal sacroiliac joints in unaffected twin (II. 2) of pair P.

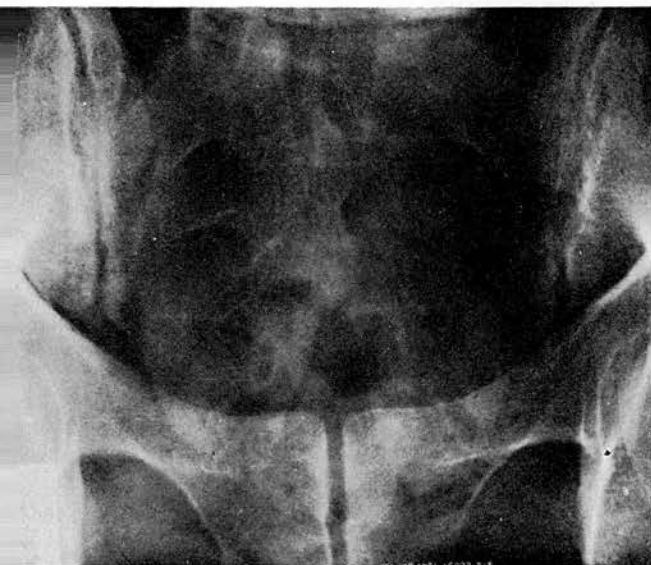


Fig. 5 Radiologically normal sacroiliac joints in unaffected twin (II. 2) of pair R.

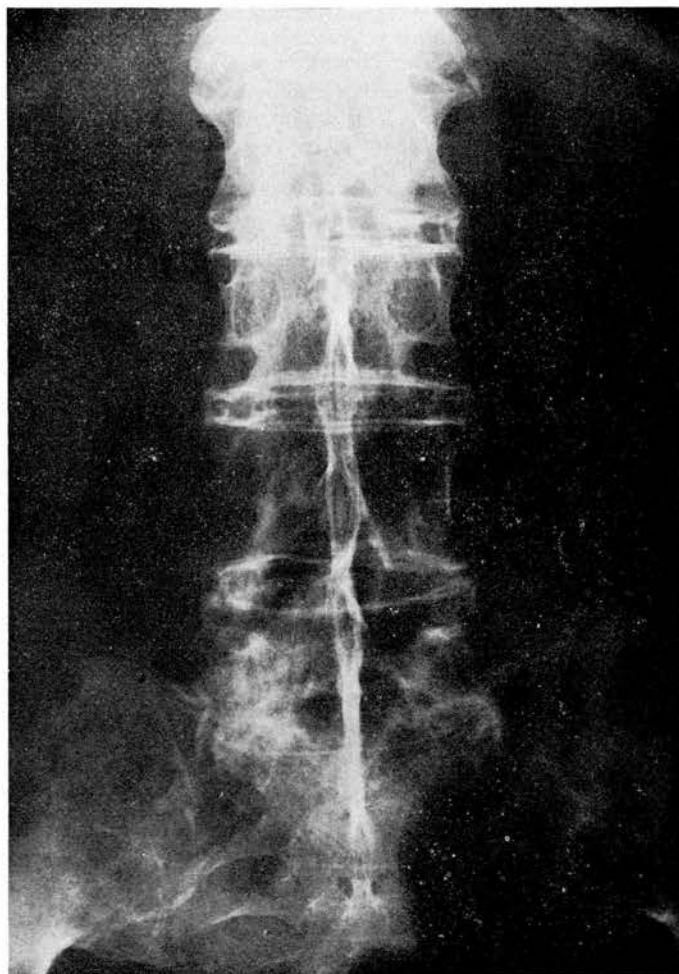


Fig. 6 Radiograph of lumbar spine and sacroiliac joints of the more severely affected twin (II. 3) of pair E, showing fusion of the sacroiliac joints and bamboo spine.

Results

The ages of the twin pairs E, P, and R were 59 years, 52 years, and 45 years respectively. The probabilities, based on red cell grouping, that they are monozygotic are 0.972, 0.956, and 0.976 respectively. The pedigrees of each pair of twins are shown in Figs. 1-3. In the pairs P and R (Figs. 1 and 2 respectively) the probands have ankylosing spondylitis but their identical twin brothers have no suggestive symptoms, normal spinal movements, and radiologically normal sacroiliac joints (Figs. 4, 5). Twins P lived in the same household until the affected twin came to live in Liverpool at the age of 32 years, which was 9 years after the onset of his back symptoms. Twins R both lived in the same household until 20 years ago.

With regard to the third twin pair (twins E; Fig. 6, 7) both lived in the same household up to the twenties. Both have radiological sacroiliitis (Figs. 6, 7), but one (II.3, Fig. 3) has severe clinical and radiological ankylosing spondylitis (Fig. 6), whereas his twin (II.2, Fig. 3) has no back symptoms and clinical or radiological spondylitis (Fig. 7). This severely affected twin has had anterior uveitis, his more severely affected twin brother has not. Both twins have affected children. Twin II.2 has a 33-year-old daughter (III.1) with a 15-year history of back pain and stiffness, some limitation of all spinal movements, a chest expansion of 4 cm, and unilateral grade 3 radiological sacroiliitis. She has also had recurrent anterior uveitis since the age of 27 years. The other twin (II.3) has a son (III.2), who was proband of this family, aged 33 years with a 15-



Fig. 7 Radiograph of lumbar spine and sacroiliac joints of the less severely affected twin (II. 2) of pair E, showing lateral grade 3 sacroiliitis without spondylitis.

tory of back pain and stiffness with marked limitation of all spinal movements, a chest expansion 3 cm, and radiological sacroiliitis and spondylitis has not had anterior uveitis.

Discussion

Twins P and R confirm that discordance for ankylosing spondylitis does occur in monozygotic twins. Since both pairs are over the age of 45 years it is unusual for symptoms or signs of ankylosing spondylitis to appear after that age there is only a remote possibility of the unaffected twins developing the disease in the future. One of Moesmann's (1960) discordant monozygotic twin pairs was aged 47 years at the ages of the other two discordant pairs were known. Persisting discordance for ankylosing spondylitis in monozygotic twins is strong evidence in favour of an environmental factor having a role in the pathogenesis of this disease.

The twin pair E is of considerable interest since

although both twins have radiological sacroiliitis the severity and extent of their disease as judged both clinically and radiologically are very different. It is possible to explain this disparity by suggesting that the lesser affected twin has ankylosing spondylitis of recent onset, but this would imply an age of onset considerably older than is considered typical. An alternative explanation is that different environmental factors, or a quantitative difference of the same environmental factor has resulted in a difference of severity of disease in these two individuals with identical genetic susceptibility.

Uveitis may occur at any age but it is notable that there is also discordance for this disease. It has been shown (Brewerton *et al.*, 1973c; Woodrow *et al.*, 1975) that HLA B27 predisposes to anterior uveitis and the discordance in these HLA B27-positive twins again implies the role of chance environmental factors in this disease.

The findings in these monozygotic twins suggest that while genetic factors are important in the pathogenesis of ankylosing spondylitis environmental factors are necessary in determining not only the initial development of the disease but possibly its future severity as well.

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HLA B27 and the genetics of ankylosing spondylitis

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SUMMARY One hundred and twenty-eight of 145 patients with ankylosing spondylitis (AS) were found to be HLA B27 positive. Five patients had evidence of a sero-negative peripheral arthritis resembling peripheral psoriatic arthritis and 3 of these were B27 negative. One further B27 negative patient had a sister with ankylosing spondylitis and ulcerative colitis and a mother with ulcerative colitis. There was evidence of a somewhat later age of onset of symptoms in B27 negative patients. These findings are interpreted as suggesting some degree of clinical and genetic heterogeneity in ankylosing spondylitis with genes for psoriasis and inflammatory bowel disease being important in some individuals, particularly those who are B27 negative.

Twenty-five first-degree relatives with ankylosing spondylitis were all B27 positive. The only instance of disassociation of B27 and spondylitis in a family was where the proband had ulcerative colitis as well as spondylitis. Of 13 B27 positive fathers 3 could be diagnosed as having definite ankylosing spondylitis (23%). These findings are thought to provide evidence against the concept that the gene for ankylosing spondylitis is not B27 but a closely linked gene and favour the occurrence of an environmental event affecting approximately one-fifth of B27 positive males to result in disease.

The finding by Brewerton *et al.* (1973) and Schlostein *et al.* (1973) of a markedly increased frequency of HLA B27 in patients with ankylosing spondylitis raises important questions concerning the genetics and pathogenesis of this disorder. The aims of the present study were to examine the relationship of B27 to ankylosing spondylitis by studying a series of patients to determine (1) if there was evidence of clinical and genetic heterogeneity in ankylosing spondylitis, (2) if dissociation of ankylosing spondylitis from B27 occurs in families, and (3) the prevalence of ankylosing spondylitis in first-degree relatives of B27 positive probands.

Patients and methods

Patients were consecutively included in the series after clinical and radiological assessment resulting in a diagnosis of definite ankylosing spondylitis as judged by the New York criteria (Bennett and Wood, 1968). Patients who were found to have psoriasis or inflammatory bowel disease or patients with spondylitis who had been ascertained through a study of patients with uveitis were excluded. Histocompati-

bility antigen typing was performed in these patients and in 451 controls who were blood donors (members of staff, using a standard microlymphocytotoxicity technique (Terasaki and McClellan 1964).

FAMILY STUDIES

These can be divided into 3 separate studies. The first was selective, in which relatives suspected of having a relevant rheumatic disease from the history given by the proband were examined clinically and radiologically and HLA typed.

The second was a clinical, radiological, and HLA typing study of parents of 20 HLA B27 positive probands, where both parents were alive and accessible. In addition, the parents of 2 further HLA B27 positive patients with ankylosing spondylitis were included because of uveitis were included. Parents were chosen for this study as all were over the age of 40 years and it is unlikely that evidence of ankylosing spondylitis will appear for the first time after this age.

Thirdly, 3 identical twins of patients with ankylosing spondylitis were examined, and the results have been previously reported (Eastmond and Woodrow, 1977).

Results

HLA TYPING

One hundred and twenty-eight of the 145 probands (88.3%) were HLA B27 positive, the control frequency being 8.97%. Twenty-two of the patients were female of whom 1 (4.5%) was B27 negative compared with 16 of the 122 males (13%). A history of acute anterior uveitis was obtained in 22 patients (15.9%) of whom 16 were male and all were B27 positive with the exception of one male patient.

PATIENTS WITH PERIPHERAL ARTHROPATHY

One B27 positive male patient had, in addition to ankylosing spondylitis, sero-positive erosive peripheral rheumatoid arthritis with a histologically confirmed rheumatoid nodule over the left olecranon process.

Two male B27 positive patients had a history of previous Reiter's disease occurring several years before the onset of the symptoms of spondylitis.

Five patients had a sero-negative peripheral small joint arthropathy with features similar to those seen in patients with peripheral psoriatic arthropathy, being B27 positive and 3 negative. The 2 B27 positive patients both gave a history of 'sausage toes' and 1 of these, who previously had onycholysis of some of the finger nails but no skin lesions, has more recently developed a small skin lesion on the right knee suggestive of psoriasis.

The 3 B27 negative patients in this category are of considerable interest. One had had episodes of 'usage fingers' and some swelling of proximal interphalangeal joints and later developed swan-neck deformity of several fingers with minimal erosive changes radiologically. The second patient has had swelling and tenderness of interphalangeal joints of the toes and his father has psoriasis with similar changes in the toes and a proximal interphalangeal joint arthropathy in the hands but no radiological croiliitis. The third patient has had an asymmetrical distal and proximal interphalangeal joint arthropathy of the hand with erosive changes in the clinically affected joints.

Two B27 positive female patients have had a mild peripheral small joint oligoarthritis with no distinctive features in respect of joints affected or clinical features of the joint involvement.

A B27 NEGATIVE PATIENTS

Three of these 17 patients are documented above. No other patients in this group are of interest. One male developed symptoms of ankylosing spondylitis at the age of 32 years and at the age of 62 years developed acute synovitis of wrists, metacarpophalangeal joints, and ankles with associated

circinate balanitis, keratoderma blennorrhagicum of the palms and soles, and conjunctivitis but no urethritis or diarrhoea. This episode resolved leaving no residua. The second patient, also male, and whose parents were first cousins had a sister with ankylosing spondylitis and ulcerative colitis and a mother with ulcerative colitis and probable ankylosing spondylitis. (Fig. 1).

The 12 remaining B27 negative patients differed in no way clinically or radiologically from the B27 positive patients. Six of these were of considerable clinical severity with radiological changes in the spine as well as in the sacroiliac joints.

AGE OF ONSET (Fig. 2)

It was possible to determine the approximate age of onset with some reasonable accuracy in 137 patients. The distribution of the age of onset in B27 negative patients was compared with that in the B27 positive patients by the Wilcoxon rank sum test. It was found that the age of clinical onset in B27 negative patients was higher overall than that in the B27 positive patients ($P=0.012$).

FAMILY STUDIES

Selected families

In the families of 22 probands all of whom were B27 positive there were 2 or more cases of ankylosing spondylitis. Four of these probands were female. All 25 clinically affected relatives of these probands were B27 positive. The only instance where an affected relative of a B27 negative proband was found is shown in Figure 1.

Figure 3 shows a family not included within the main series because the B27 negative proband had ulcerative colitis in addition to ankylosing spondylitis

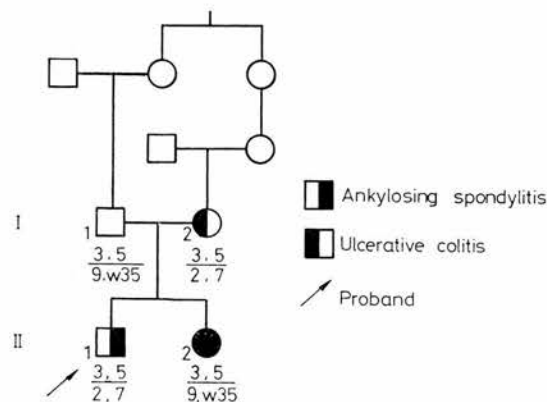


Fig. 1 Pedigree of the family of a B27 negative patient with ankylosing spondylitis.

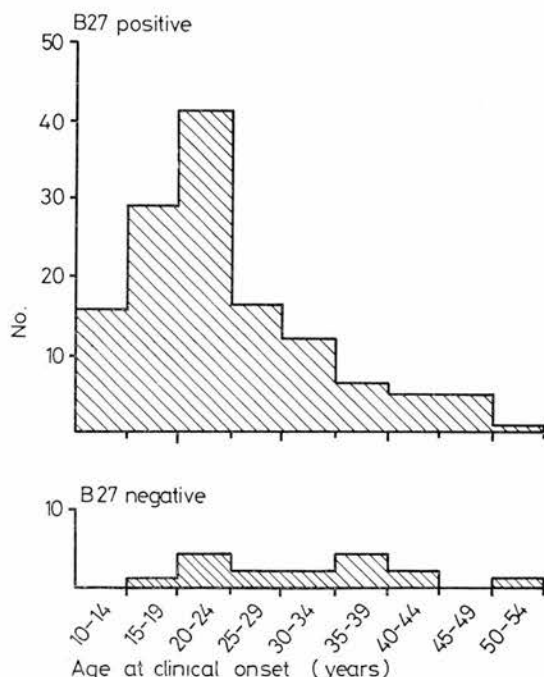


Fig. 2 Distribution of age at onset of symptoms in B27 positive and B27 negative patients with ankylosing spondylitis.

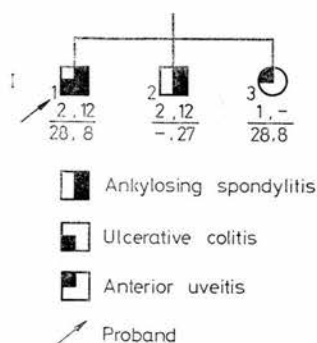


Fig. 3 Pedigree of the family of a B27 negative patient with ankylosing spondylitis and ulcerative colitis showing an affected B27 positive proband.

A brother was found to be B27 positive and had ankylosing spondylitis and a sister was B27 negative and gave a history of acute anterior uveitis. This was the only example encountered in the study of 2 first-degree relatives with spondylitis, one being B27 positive and the other negative.

Study of parents

Thirteen of the 22 fathers and 12 of the 22 mothers of 22 HLA B27 positive probands were found to be HLA B27 positive. Of these parents, 2 fathers were known to have clinical and radiological ankylosing spondylitis and 1 father had asymptomatic grade 3 radiological sacroiliitis and spondylitis with limited spinal movements and diminished chest expansion. Two fathers had asymptomatic grade 3 radiological sacroiliitis. Thus 3 out of 13 (23.1%) B27 positive fathers could be diagnosed as having ankylosing spondylitis. No clinical or radiological evidence of disease was found in the HLA B27 positive mother or in the HLA B27 negative parents.

Identical twins

A study of 2 identical twins of probands with ankylosing spondylitis revealed no clinical or radiological evidence of ankylosing spondylitis or related diseases. Their ages were 45 and 52 years, respectively. The identical twin aged 59 of a further patient with severe ankylosing spondylitis had a history of 1 episode of acute anterior uveitis and radiologically had a unilateral grade 3 sacroiliitis but no rheumatic symptoms (Eastmond and Woodrow, 1977).

Discussion

The association between ankylosing spondylitis and HLA B27 raises two main and related questions. The first is whether the major gene underlying susceptibility to the disease (the AS gene) is B27 itself or whether it is not B27 but a gene which is at a locus very close to the HLA B locus and which is in very strong linkage disequilibrium with B27.

The second and related question is whether the spondylitis in B27 negative individuals is genetically the same as in B27 positive subjects, i.e. that the AS gene is the same for both groups and is therefore not B27.

B27 ITSELF *versus* LINKED AS GENE

A strong possibility in regard to most HLA disease associations is that the disease susceptibility gene may not be the particular HLA A or B locus genes found to be associated with the disease but a gene at a closely linked locus in linkage disequilibrium with the A and B locus genes. However, the relative risk for ankylosing spondylitis in B27 positive individuals when estimated from combined data (76 (Woodrow, 1977)), this being considerably higher than for any other HLA and disease association.

If the HLA linked AS gene were not B27 itself, the findings might be expected. The first is that aggregation of B27 negative individuals with spondylitis should occur in families to the same degree as observed in the case of B27 positive patients. So far,

no pair of B27 negative first-degree relatives with spondylitis appears to have been documented. The only instance we have observed is the family shown in Fig. 1 in which ulcerative colitis was present in 1 of the 2 affected B27 negative sibs and in their mother. It is of interest that the parents in this family were related, suggesting the possibility of a recessive trait predisposing to the inflammatory bowel disease and spondylitis. Another interesting family in which a B27 negative spondylitic was the offspring of a consanguineous marriage was reported by Van der Linden *et al.*, (1975).

Secondly, one might expect to see examples of disassociation of B27 from ankylosing spondylitis within a family, ie, evidence of recombination between the B locus and the supposed locus for the AS gene. Two families have been reported (Dick *et al.*, 1975; Strosberg *et al.*, 1975) in which apparent disassociation of spondylitis from B27 has occurred. In these instances genetic recombination would be the explanation if it were certain that other, non-HLA linked genes predisposing to spondylitis were not segregating in the families.

The only occasion on which this phenomenon was observed in the present study was in a family shown in Fig. 3 where the B27 negative patient with spondylitis also had ulcerative colitis.

The demonstration of genetic recombination classically depends on the certain identification of the presence or absence of relevant segregating genes and thus it is relatively easy for traits showing simple Mendelian inheritance, ie, the presence of a particular phenotype must imply the presence of one particular gene. This does not necessarily apply to conditions with a possible heterogeneous genetic basis and where the trait does not invariably appear in the genetically predisposed.

Further information on this point may be obtained by studying the prevalence of ankylosing spondylitis in B27 positive persons in the general population compared with B27 positive relatives of ankylosing spondylitis probands. Evidence has been produced that something of the order of 20% of B27 positive individuals develop ankylosing spondylitis in some degree (Calin and Fries, 1975; Truog *et al.*, 1975; Cohen *et al.*, 1976). It is of interest to compare this figure with that for the incidence of disease in B27 positive first-degree relatives of B27 positive probands. If indeed the 20% incidence claimed is the true figure for the general population it could arise in three main ways. The first is that the AS gene is B27 and a separate gene segregating independently of the HLA system and present in homozygous or heterozygous state (depending on whether the effect is as a recessive or dominant trait) is also necessary to produce the complete genotype for the disease. If

this were true one would expect that, for a dominant interacting gene, 50% of first-degree B27 positive relatives would develop spondylitis and, for a recessive trait, approximately 25% of B27 positive sibs and a considerably lower frequency of parents would develop disease. Secondly, B27 might be the AS gene and an environmental factor randomly affecting 20% of the population is necessary for the disease to develop. This would result in a similar prevalence of disease in B27 positive relatives of probands as in B27 positive persons in the general population, ie 20%, unless these relatives are more liable to be exposed to an important environmental agent. The third possibility is that the AS gene is not B27 but is present on approximately 20% of chromosomes which have the B27 gene. In this case all B27 positive first-degree relatives would be expected to have this gene and to develop disease to some degree.

The finding of ankylosing spondylitis in 23.1% of B27 positive fathers in the present study may be compared with the figure given above for the general population. The fact that these are of a similar order is strongly against a linked AS gene on 20% of B27 positive chromosomes, and is most in keeping with the result expected with the second proposal of a random environmental factor affecting 20% of the population. However, this approach requires further investigation using identical criteria for the study of the general population and the families. Discordance in identical twins is also supportive evidence for environmental factors affecting the prevalence of disease in genetically predisposed individuals.

The absence of clinical and radiological abnormalities in any of the B27 positive mothers studied so far supports previous general experience of the sex distribution of the disease and is difficult to reconcile with the findings of Calin and Fries (1975) who in their study of a population of B27 positive individuals found approximately equal numbers of males and females with evidence of spondylitis.

B27 POSITIVE SPONDYLITIS *versus* B27 NEGATIVE SPONDYLITIS

In regard to the previous discussion it is of some interest to know if there is evidence for heterogeneity within the disease ankylosing spondylitis, as this may have a bearing on the way we may attempt to determine the nature of the AS gene.

CLINICAL EVIDENCE

It has been suggested that the disease takes a milder and more localised course in B27 negative patients. Thus Möller and Olhagen (1975) found all 66 patients with radiologically demonstrable syndesmophytes to be B27 positive, in contrast with 70% of 60 patients

with sacroiliitis as the only radiological manifestation. Feldmann *et al.* (1975) found 6 B27 negative patients amongst 25 with milder disease and only 1 of 25 with moderate or severe disease. However, Van den Berg-Loonen *et al.* (1977) found 4 of 20 patients with spinal involvement to be B27 negative and Jeannot *et al.* (1975) found 3 B27 negative patients among 14 females with radiological involvement of the spine. In the present series the 17 B27 negative patients had clinical and radiological involvement as severe as was found in the B27 positive patients. One possibility is that patients with sacroiliitis only are aetiologically more heterogeneous than those with spinal changes and it is of interest that Dekker-Saeyns *et al.* (1978) described 11 patients with ulcerative colitis who had asymptomatic radiological sacroiliitis and of these only 1 was B27 positive.

With regard to peripheral arthritis, 3 of the B27 negative patients in the present study had an arthropathy with features strongly suggestive of psoriatic arthropathy but in the absence of psoriasis. It has been shown that patients with psoriatic peripheral arthritis and ankylosing spondylitis are less frequently B27 positive than patients with ankylosing spondylitis alone (reviewed in Woodrow, 1977). The implication is that genes for psoriasis may be playing a role in the pathogenesis of spondylitis in these cases, a conclusion also drawn from a study of the arthropathies occurring in patients with psoriasis (Eastmond and Woodrow, 1977).

The fact that B27 negative patients tend to have a somewhat higher age of onset of symptoms supports the thesis of aetiological heterogeneity between the two groups.

As mentioned above, no examples of ankylosing spondylitis occurring in 2 B27 negative relatives has been reported previously. The only example seen by us was a family in which there could be genes for ulcerative colitis predisposing to the development of ankylosing spondylitis. This explanation is supported by the fact that patients with ulcerative colitis and ankylosing spondylitis are less frequently B27 positive than those with ankylosing spondylitis alone (Brewerton *et al.*, 1974). The family shown in Fig. 3 also gives credence to this argument. The brother without ulcerative colitis could be considered as dependent upon being B27 positive in order to develop ankylosing spondylitis whereas the proband with ulcerative colitis was able to develop equally severe spinal disease in the absence of B27.

CONCLUSIONS

(1) Present evidence favours the gene for ankylosing spondylitis being the HLA B27 gene itself and the

results of present study would be against the linked gene hypothesis.

(2) There is some evidence that ankylosing spondylitis is genetically heterogeneous and that in HLA B27 negative persons it differs from the disease in HLA B27 positive persons by (a) having a later mean age of onset, (b) having, in some cases, features of psoriatic peripheral arthritis, and (c) having, in some cases, evidence for genes for ulcerative colitis predisposing to spinal disease.

(3) The present study does not support the suggestion that ankylosing spondylitis is less severe in HLA B27 negative patients than HLA B27 positive ones, when no associated disease is present.

ASSOCIATION WITH OTHER ARTHROPATHIES

The single case of sero-positive rheumatoid arthritis is considered to represent the coincident occurrence of the separate conditions in the same individual. The two instances where Reiter's disease had occurred before the onset of symptoms of spondylitis probably represent the occurrence of two diseases provoked in the same genetically predisposed individuals by different environmental agents. Instances where Reiter's disease occurred in patients who already had ankylosing spondylitis have been previously reported (Woodrow *et al.*, 1974).

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